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Acute Pancreatitis, Updated Best Practices Based Management Compared to Professional Guidelines Statements: Literature Review & Recommendations

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Abstract

Objectives: Several clinical guidelines exist for acute pancreatitis, with varying recommendations. The aim of this study is to determine the quality of guidelines for acute pancreatitis and comparison to the updated best practices. Finally suggestion of best way of clinical management.

Methods: First, literature search has identified relevant acute pancreatitis management guidelines, were then reviewed to determine their document format and scope and the presence of endorsement by a professional body. The quality of fifty five guidelines is determined using the validated "Grading of Recommendations Assessment, Development and Evaluation" hierarchy of evidence. The second, literature review for updated best practices' management of acute pancreatitis and related complications. Finally, proposal for a structured best results' management proposal for acute pancreatitis has been achieved.

Results: Fifty five guidelines endorsed by professional bodies are analyzed regarding evidence quality that is found not improved over time. Guidelines with tables, a recommendations summary, evidence grading, and audit goals had significantly higher scores than guidelines lacking those features. Guidelines have not been a sharp cut for decision making regarding diagnosis, prediction of complication or treatment in addition of being not strictly followed. Updated best practices have accumulated over time and postulated a new conceptual approach competency.

Conclusion: The many clinical guidelines for acute pancreatitis range widely regarding statements' quality. Updated best practices management procedures for acute pancreatitis should be observed by professional bodies to consider valued one into the guidelines. Further dynamic wide scale research is required to determine whether guideline quality alters clinical outcomes.

Keywords: Guideline for acute pancreatitis; Hepato-bilio-pancreatic professional bodies; Grading of Recommendations Assessment Development and Evaluation (GRADE); Sequential organ failure assessment (SOFA); Determinant-Based Classification for the severity (DBC); Visual Analogue Scale (VAS)

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Methodology & Aim of Research

Search strategy

This systematic review is conducted in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta Analyses" (PRISMA) guidelines. The Cochrane Library, Ovid, PubMed and Embase are searched for the following keywords:

- Guidelines and extracted statements for management of acute pancreatitis;
- Professional bodies for hepato-bilio-pancreatic specialty;
- Grading of Recommendations Assessment Development and Evaluation (GRADE);
- Best clinical practices in the management of acute pancreatitis;
- Sequential Organ Failure Assessment (SOFA) in acute pancreatitis;
- Determinant-Based Classification for the severity (DBC) of acute pancreatitis;

- Visual analogue scale (VAS) in acute pancreatitis.

Publications between January 1st, 1900 and October 30th, 2020 are included using search filters. For repeated article content the most recent covering articles are included with exclusion of that of previous date. Original articles and reviews are included with Cochrane Library, Ovid, PubMed and Embase filters.

Literature Review

All citations were managed in Microsoft Excel. Duplicate publications were removed. The three authors have reviewed all abstracts. Inclusion criteria were as follows: Initial publication date after January 1st, 1900 through October 30th, 2020; reporting on acute pancreatitis management including diagnosis and treatment are all collected. Exclusion criteria included articles not available in English. All discrepancies were resolved through discussion among the three authors. Full-length articles were reviewed by all authors for inclusion in the systematic review.

Aim of Article

The main aim of this article is to present a contemporary review on the clinical evidence supporting the current clinical situation and the prospective advances regarding best practices in the management of acute pancreatitis.

Introduction

Acute Pancreatitis (AP) is one of the top ten most common diagnoses at discharge for gastrointestinal diseases, and there is a global trend toward an increasing incidence. Numerous challenges and controversies remain unresolved in disease management, including how best to predict organ failure, the use and timing of diagnostic tests, and the type and timing of surgical intervention. Therefore, clinical practice guidelines exist for AP to aid clinical decision making, and there is consensus between them in some areas and a lack of consensus in other areas [1-4].

Clinical practice guidelines have been defined by the Institute of Medicine as systematically developed evidenced statements about appropriate health care decision taking for specific clinical circumstances. Compliance with guidelines should be consistent with best practice, with implications for resources' allocation, insurance claims and premiums, and litigation [5-8].

Exploitation

High-quality guidelines (defined as conferring the confidence that the potential biases inherent of guideline development have been addressed adequately and that the recommendations are both internally and externally valid and are practically feasible) are developed by transparent well-defined methodology, with clearly identified and appropriate evidence in support to each recommendation [9].

Based on this, the following recommendations are made regarding the development of guidelines for AP:

- Guidelines should have official endorsement from a professional body who should consider appointing 1) independent methodologists who perform the systematic reviews, synthesis of the evidence, and formulation of recommendations with evidence grading, and 2) professional experts to define the clinical questions and guideline scope, and to raise questions related to clinical implications and implementation of evidence (7).

- Multiple disciplines should structure the guidelines' development where the rationale helps to ensure all relevant stake-holders are involved; reducing the potential for bias.

- The guidelines' format should include summary tables obviating 1) crucial information, summary of the recommendations facilitating their identification, 2) evidence grading to allow clinicians to evaluate recommendations' strength and finally 3) goals enabling centers to objectively assess their patient management against current evidence.

In relation to AP guidelines vary greatly in format, scope, and quality, have not improved in quality over time, so that until now there is no unified global agreement on a single guideline.

AP is pancreatic inflammatory condition that mostly takes a mild course, where moderate fluid resuscitation, management of pain and nausea, and early oral feeding result in rapid clinical improvement. Severe Acute Pancreatitis (SAP) comprises for about 20% to 30% of cases, is a life-threatening disease with hospital mortality rates of about 15%. The most commonly used classification system for AP is the 2012 revision of the Atlanta classification and definitions based on international consensus. This classification identifies two phases (early and late). Severity is classified as mild, moderate, or severe. The mild form (interstitial edematous pancreatitis) has no organ failure, local or system complications, and usually resolves in the first week. If there is transient (less than 48 h) organ failure, local complications or exacerbation of co-morbid disease, it is classified as moderate and with persistent (more than 48 h) organ failure, it is the severe form. Infection of the pancreatic and peripancreatic necrosis occurs in about 20% to 40% of patients with SAP, and is associated with worsening organ dysfunctions. The mortality rate in patients with infected necrosis and organ failure occurs in about 35% while concomitant sterile necrosis and organ failure is associated with a mortality of about 20%. If the infected necrosis without organ failure, the mortality is ranging between 1% to 2%. Pancreatic necrosis/collection has two phases; the peripancreatic collections associated with necrosis are Acute Necrotic Collection (ANC); that presents during the first 4 weeks and containing variable amount of fluid and necrotic tissue involving the pancreatic parenchyma and/or peripancreatic tissues and Walled-Off Necrosis (WON); that is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with a well-defined, enhancing inflammatory wall that takes usually 4 weeks or more after the onset of AP [10-12].

Currently, several trends in the management of SAP have changed our clinical practices; early enteral feeding, selective role of prophylactic antibiotics, avoiding surgery in patients with sterile necrosis, more conservative approach to infected necrosis with delayed intervention, whether endoscopic or surgical, and management of biliary pancreatitis.

The most popular guidelines for acute pancreatitis are hereby mentioned below;

- 2019 WSES guidelines for the management of severe acute pancreatitis [13].

- The consensus of integrative diagnosis and treatment of acute pancreatitis 2017 [14].

- Japanese guidelines 2015 for the management of acute pancreatitis [15].

- Revised Japanese guidelines for the management of acute

pancreatitis 2015 [16].

- American College of Gastroenterology guidelines for management of acute pancreatitis 2013 [17].
- Classification of acute pancreatitis 2012: Revision of the Atlanta classification and definitions by international consensus [10].
- The international consensus diagnostic criteria for autoimmune pancreatitis; guidelines of the International Association of Pancreatology 2011 [18].

Generally, guidelines have been created by international collaboration and discussion among an expert panel of clinicians, practicing in the field of emergency surgery and managing patients with severe acute pancreatitis. Consensus guidelines have been facilitated by the World Society of Emergency Surgery, and are an update of the 2014 World Society of Emergency Surgery (WSES) position paper on this topic. In our research we have reviewed the statements and formulated and graded them according to the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) hierarchy of evidence from Guyatt et al. [19,20].

"GRADE" system scoring details

1A = Strong recommendation with strong evidence,

1B = Strong recommendation with moderate evidence,

1C = Strong recommendation with weak evidence,

2A = Weak recommendation with strong evidence,

2B = Weak recommendation with moderate evidence, and

2C = Weak recommendation with weak evidence.

For clarity, the statements and discussions have been divided into five topics: Diagnosis, Antibiotic treatment, Management in the Intensive Care Unit (ICU), Surgical and operative management, and Open abdomen [20].

Professional bodies' guidelines for diagnosis, prognosis and management of acute pancreatitis statements (fifty-five statements) have been classified under four categories and demarcated with their evidence grades as documented below:

Diagnostic & Prognostic statements

Statements for diagnostic imaging:

1. On admission, Ultrasound (US) should be performed to determine the etiology of AP (biliary) (1C).
2. When doubt exists, Computed Tomography (CT) provides good evidence of the presence or absence of pancreatitis (1C).
3. All patients with SAP need to be assessed with Contrast-Enhanced Computed Tomography (CE-CT) or Magnetic Resonance Imaging (MRI). Optimal timing for first the CE-CT assessment is 72 h to 96 h after onset of symptoms (1C).
4. Magnetic Resonance Cholangio Pancreatography (MRCP) or endoscopic ultrasound should be considered to screen for occult common bile duct stones in patients with unknown etiology (1C).

Statements for diagnostic laboratory parameters:

1. The cut-off value of serum amylase and lipase is normally defined to be three times the upper limit (2A).
2. C-reactive protein level ≥ 150 mg/l at third day can be used as a prognostic factor for SAP (2A).
3. Hematocrit >44% represents an independent risk factor of pancreatic necrosis (1B).
4. Urea >20 mg/dl represents itself as an independent predictor of mortality (2B).
5. Procalcitonin is the most sensitive laboratory test for detection of pancreatic infection, and low serum values appear to be strong negative predictors of infected necrosis (2A).
6. In the absence of gallstones or significant history of alcohol use, serum triglyceride and calcium levels should be measured. Serum triglyceride levels over 11.3 mmol/l (equals to 1000 mg/dl) indicate it as the etiology (2C).

Statements for diagnostics in idiopathic pancreatitis: In idiopathic pancreatitis, biliary etiology should be ruled out with two ultrasound examinations, and if needed MRCP and/or endoscopic ultrasound EUS, to prevent recurrent pancreatitis (2B).

Statements for AP severity grading:

1. SAP is associated with persistent organ failure (cardiovascular, respiratory, and/or renal), and high mortality (1A).
2. Patients who have persistent organ failure with infected necrosis have the highest risk of death (1C).
3. Patients with organ failures should be admitted to an intensive care unit whenever possible (1 C).

Statement for risk development scoring: There are no "gold standard" prognostic score for predicting SAP. Probably the "Bedside Index of Severity of Acute Pancreatitis" (BISAP) score is one of the most accurate and applicable in everyday clinical practice because of the simplicity and the capability to predict severity, death, and organ failure as well as the APACHE-II and other scores (1B).

Conservative therapeutic management statements

Statements for follow-up imaging:

1. In SAP (computed tomography severity index ≥ 3), a follow-up CECT scan is indicated 7 to 10 days from the initial CT scan (1C).
2. Additional CE-CT scans are recommended only if clinical status deteriorates or fails to show continued improvement, or when invasive intervention is considered (1C).

Statement for usage of prophylactic antibiotics: Recent evidences have shown that prophylactic antibiotics in patients with AP are not associated with a significant decrease in mortality or morbidity. Thus, routine prophylactic antibiotics are no longer recommended for all patients with AP (1A).

Statement for infected necrosis prediction and treatment:

1. Antibiotics are always recommended to treat infected SAP. However the diagnosis is challenging due to the clinical picture that cannot be distinguished from other infectious complications or from the inflammatory status caused by AP (2A).
2. Serum measurements of "Procalcitonin" (PCT) may be valuable in predicting the risk of developing infected pancreatic necrosis (2B).

3. A CT-guided "Fine-Needle Aspiration" (FNA) for Gram-stain and culture can confirm an infected SAP and drive antibiotic therapy but is no longer in routine use (2B).

Statement for type of antimicrobials: 1. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis should be used (2B).

1. In patients with infected necrosis, the spectrum of empirical antibiotic regimen should include both aerobic and anaerobic Gram-negative and Gram positive microorganisms. Routine prophylactic administration of antifungal is not recommended in patients with infected AP, although *Candida* spp. are common in patients with infected pancreatic necrosis and indicate patients with a higher risk of mortality (2B).

Statement for vital signs monitoring: Continuous vital signs monitoring in high dependency care unit is needed if organ dysfunction occurs. Persistent organ dysfunction or organ failure occurrence despite adequate fluid resuscitation is an indication for ICU admission (1C).

Statement for timing and type of fluid resuscitation: Early fluid resuscitation is indicated to optimize tissue perfusion targets, without waiting for hemodynamic worsening. Fluid administration should be guided by frequent reassessment of the hemodynamic status, since fluid overload is known to have detrimental effects. Isotonic crystalloids are the preferred fluid (1B).

Statement for pain control: No evidence or recommendation about any restriction in pain medication is available. "Nonsteroidal Anti-Inflammatory Drugs" (NSAID) should be avoided in Acute Kidney Injury (AKI). Epidural analgesia should be an alternative or an agonist with intravenous analgesia, in a multimodal approach.

Patient-Controlled Analgesia (PCA) should be integrated with every described strategy. Dilaudid is preferred over morphine or fentanyl in the non-intubated patient (1C).

Statement for management of increased intra-abdominal pressure: Limitation of sedation, fluids, and vasoactive drugs to achieve resuscitative goals at lower normal limits is suggested. Deep sedation and paralysis can be necessary to limit intra-abdominal hypertension if all other non-operative treatments including percutaneous drainage of intraperitoneal fluid are insufficient, before performing surgical abdominal decompression (1B).

Statement for mechanical ventilation: Mechanical ventilation must be instituted if oxygen supply, even with high flow nasal oxygen, or continuous positive airway pressure became ineffective in correcting tachypnea and dyspnea.

Both non-invasive and invasive techniques can be used, but invasive ventilation is mandatory when bronchial secretions clearance start to be ineffective and/or the patient is tiring of predicted to tire. Lung-protective strategies should be used when invasive ventilation is needed (1C).

Statement for pharmacological treatment: No specific pharmacological treatment except for organ support and nutrition should be given (1B).

Statement for enteral nutrition: Enteral nutrition is recommended to prevent gut failure and infectious complications. Total Parenteral Nutrition (TPN) should be avoided but partial parenteral nutrition integration should be considered to reach caloric and protein requirements if enteral route is not completely tolerated. Both gastric and jejunal feeding can be delivered safely (1A).

Minimal access interventional therapeutics statements

Statements for emergent "endoscopic retrograde cholangiopancreatography" ERCP indications:

1. Routine ERCP with acute gallstone pancreatitis is not indicated (1A).

2. ERCP in patients with acute gallstone pancreatitis and cholangitis is indicated (1B).

3. ERCP in acute gallstone pancreatitis with common bile duct obstruction is indicated (2B).

4. ERCP in patients with predicted severe acute gallstone pancreatitis without cholangitis or common bile duct obstruction cannot be recommended at this time (2B).

Statement for percutaneous/endoscopic drainage of pancreatic collections indications: Clinical deterioration with signs or strong suspicion of infected necrotizing pancreatitis is an indication to perform intervention (percutaneous/endoscopic drainage) after 4 weeks after the onset of the disease:

- On-going organ failure without sign of infected necrosis.
- On-going gastric outlet, biliary, or intestinal obstruction due to a large walled off necrotic collection.
- Disconnected duct syndrome.
- Symptomatic or growing pseudocyst.

After 8 weeks from the onset of disease:

- On-going pain and/or discomfort (1C).

Surgical intervention statements

Statements for surgical intervention indications:

The following are indications for surgical intervention:

- As a continuum in a step-up approach after percutaneous/endoscopic procedure with the same indications.
- Abdominal compartment syndrome.
- Acute on-going bleeding when endovascular approach is unsuccessful.
- Bowel ischemia or acute necrotizing cholecystitis during AP.

1. Bowel fistula extending into a peripancreatic Collection (1C).

Statements for defining surgical strategy: 1. In infected pancreatic necrosis, percutaneous drainage as the first line of treatment (step-up approach) delays the surgical treatment to a more favorable time or even results in complete resolution of infection in 25% to 60% of patients and it is recommended as the first line of treatment (1A).

2. Minimally invasive surgical strategies, such as trans-gastric endoscopic necrosectomy or "Video Assisted Retroperitoneal Debridement" (VARD), result in less postoperative new-onset organ failure but require more interventions (1B).

3. Considering mortality, there is insufficient evidence to support

open surgical, mini-invasive, or endoscopic approach (1B).

4. In selected cases with walled-off necrosis and in patients with disconnected pancreatic duct, a single stage surgical trans-gastric necrosectomy is an option (2C).

5. A multidisciplinary group of experts should individualize surgical treatment taking local expertise into account (2C).

Statement for surgery timing: 1. Postponing surgical interventions for more than 4 weeks after the onset of the disease results in less mortality (2B).

Statements for cholecystectomy surgery timing: 1. Laparoscopic cholecystectomy during index admission is recommended in mild acute gallstone pancreatitis (1A).

2. When ERCP and sphincterotomy are performed during the index admission, the risk for recurrent pancreatitis is diminished, but same admission cholecystectomy is still advised since there is an increased risk for other biliary complications (1B).

3. In acute gallstone pancreatitis with peripancreatic fluid collections, cholecystectomy should be deferred until fluid collections resolve or stabilize and acute inflammation ceases (1C).

Statements for open abdomen indication: 1. In patients with SAP unresponsive to conservative management of Intra-Abdominal Hypertension (IAH) and Abdominal Compartment Syndrome (ACS), surgical decompression and use of open abdomen are effective in treating the abdominal compartment syndrome (2C).

2. We suggest that clinicians should be cautious not to over-resuscitate patients with early SAP and measure intra-abdominal pressure regularly (1C).

3. We suggest that the open abdomen (OA) be avoided if other strategies can be used to mitigate or treat severe intra-abdominal hypertension in SAP (1C).

4. We recommend not utilizing the OA after necrosectomy for SAP (unless severe IAH mandates OA as a mandatory procedure) (1C).

5. We recommend not to debride or undertake early necrosectomy if forced to undertake an early OA due abdominal compartment syndrome or visceral ischemia (1B).

Statements for open abdomen management and temporary abdominal closure: 1. We recommend the use of Negative Pressure Peritoneal Therapy (NPPT) for OA management (1B).

2. We suggest fascial traction be added to Negative Pressure Wound Therapy (NPWT) methods (2B).

3. Further controlled studies should be conducted on Intra-Peritoneal Osmotic Therapies (IPOT) in SAP (no recommendation).

Statement for timing of dressing changes: 1. Open abdomen re-exploration should be conducted no later than twenty four to forty eight hours after the index and any subsequent operation, with the duration from the previous operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (1C).

To summarize, these guidelines present evidence-based international consensus statements on the management of AP specially the severe form, from collaboration of a panel of experts. It contains fifty five statements on diagnosis, management in the ICU, surgical and operative management, open abdomen, and antibiotic treatment. For some of the statements such as severity grading, imaging, use of prophylactic antibiotics and most aspect of the management in the ICU, the evidence is strong. For others, such as laboratory diagnostics and surgical strategies, for example, the evidence is quite weak requiring further studies. That is why clinician's commitment with these statements is not as high as needed. With accumulating knowledge, these statements need to be regularly updated and refined to include only the high evidenced ones [13].

Updated best clinical practices for AP management

Acute pancreatitis definition: AP is defined as the acute inflammation of the pancreas, leading to systemic and local complications, including pancreatic edema, necrosis, hemorrhage or infection, accompanied with peripancreatic fluid collections, Walled-Off Necrosis (WON), and organ dysfunction or failure outside the pancreas. On the basis of the etiology, AP can be classified as Acute Biliary Pancreatitis (ABP), alcohol-related pancreatitis, hyperlipidemic pancreatitis, wounded pancreatitis, drug-related pancreatitis, pregnancy pancreatitis, and so on. According to the presence and duration of organ failure and complication, it is divided into three types: Mild Acute Pancreatitis (MAP), Moderate-Severe Pancreatitis (MSAP), and Severe Acute Pancreatitis (SAP). In addition, the Determinant-Based Classification for the severity (DBC), based on the occurrence and duration of organ failure, pancreatic necrosis, and secondary infections, is also considered and applied [1,21-28].

Clinical presentation

1. Symptoms

Patients with AP typically present with acute epigastric pain. The pain is described as lasting, intense, and unbearable. The location of the pain can affect the bilateral ribs, even radiating to the back of the waist. Patients with AP also commonly suffer from nausea, vomiting, abdominal distension, constipation, and less yellow urine, even anuria. Patients with AP may accompany with fever, cold or chills, and jaundice. Moreover, these symptoms, such as dyspnea, nervousness, palpitations, inability to lie down, restlessness, limbs coldness, oliguria or anuria, gibberish, lethargy, gastrointestinal bleeding, and so on, may be manifested in severe cases [22,29].

2. Signs

The MAP only performs mild epigastric tenderness, whereas SAP accompanies with tenderness, rebound tenderness, and muscle tension in the upper or whole abdomen. Some of critically ill patients present abdominal distension, blue-purple ecchymoses, abdominal mass, intestinal type or peristaltic wave, abdominal wall varicose veins, and other performance. The blue-purple ecchymoses can be found at umbilical or bilateral abdominal subcutaneous, medial and lateral thighs, lumbar rib, or scrotum [23,30].

Related investigations

1. Laboratory routine examination

Laboratory examinations should be conducted for all patients after admission. The routine laboratory parameters include pancreatic enzymes, routine blood test, liver and renal function, blood lipid, blood glucose, electrolytes, routine stool and urine test, arterial blood gas, serum tumor markers, such as CEA, AFP, CA19-9, CA125, glycated Hemoglobin (HbA1c), fasting insulin, and C-peptide, serum

inflammatory cytokines IL-6, IL-10, CRP, and Pro-Calcitonin (PCT). When the infection is still suspected in patients with AP, the bacterial cultures of blood, drainage, and sputum are recommended [1,23].

Radiologic imaging examination: For all patients who are diagnosed with AP or suspected of AP, abdominal imaging is useful to detect the pancreatic and peri-pancreatic changes and to screen the biliary tract disease. When a doubt regarding the diagnosis of AP still exists by abdominal imaging, the use of Computed Tomography (CT) for the whole abdomen and lower chest is recommended to confirm the diagnosis. The second CT scan within the first week is unwarranted. When the patients suffer from AP for 1 week (especially within 48 h), the contrast-enhanced CT is only recommended to identify vascular lesions, such as abdominal vein thrombosis and strangulated intestinal obstruction. When patients accompany with elevated liver enzymes, with suspicious biliary stones or obstruction, with not confirmed information by ultrasonography, or with no obvious abnormalities in ultrasound, the Magnetic Resonance Cholangiopancreatography (MRCP) or Endoscopic Retrograde Cholangiopancreatography (ERCP) is recommended, but the routine use of diagnostic ERCP examination is unwarranted [1,23].

Special examination: For patients who have undergone surgical management Or Percutaneous Catheter Drainage (PCD), the routine uses of occult blood test, drainage fluid enzymatic tests, chyluria tests, and biochemical tests of abdominal drainage fluid are recommended. When patients have undergone ERCP, it is time to perform drainage fluid (bile) culture. If the intra-abdominal infection is suspected, it is critical to undergo bacterial culture of specimens after the first percutaneous puncture or surgery as soon as possible. When chronic pancreatitis is suspected in patients with autoimmune diseases, the detection of serum IgG4 levels together with pancreatic histopathology is recommended [1,23].

Procedures of diagnosis

When the patient with abdominal pain is suspicious of AP, there are five steps to judge as follows: First, it is critical to confirm whether the existence of AP or not; second, based on the complications, organ function, and pancreatic morphology, disease episodes are dynamically evaluated to classify the severity and evaluate the prognosis; third, potential etiologies are critical to being screened, such as biliary factors (biliary stones, infection, and obstruction), the tumors factors (pancreas, biliary, duodenal, and periampullary), and other factors, like hyperlipidemia; fourth, it is critical to recognize the exists of comorbidities or underlying diseases; fifth, AP is differentiated from chronic pancreatitis [1,23].

Diagnostic criteria: AP is diagnosed by typical clinical symptoms, signs, laboratory tests, and/or imaging examinations: 1) the typically abdominal pain consistent with AP, 2) serum lipase activity and/or amylase greater than three times than the upper limit of normal, and/or 3)characteristic findings from abdominal imaging, contrast-enhanced computed tomographic, and Magnetic Resonance Imaging (MRI). When a doubt regarding the diagnosis of AP still exists by clinical presentation, routine laboratory serum parameters, and abdominal imaging, the use of CT for the whole abdomen is recommended to confirm the diagnosis [1,23].

Determinants of pancreatitis severity: According to the Revision of The Atlanta Classification-2012 severity grading standard for AP; two phases of AP are recognized: early phase (1 to 2 week of onset) and late phase (after 1 to 2 week of onset). MAP and SAP are differentiated based on whether there is organ failure within 24 h after admission (Marshall score 2 points) or not. MSAP and SAP are differentiated based on whether organ failure can recover within 48 h or not. In the early stage, organ function damages/failures are used to classify the disease severity. In the late stage, the pancreatic/pancreatic morphological criterion is used as the basis for severity classification to guide treatment. Meanwhile, severity assessment indicators such as DBC, Ranson, APACHE II, Balthazar CT classification, modified CT severity index, CRP, bedside severity assessment index, and harmless AP score can also be applied [28].

Proposal of determinants-based classification of AP severity: Based on the concepts discussed; a new classification of severity for AP is devised and a proposal published. There is no a prior decision or rationale regarding the number of categories. The starting point is to determine, using the well-accepted concept of causal inference, what factors had a cause-effect relationship with severity, as opposed to non-causal associations. Two factors are identified as being principle determinants of severity: Local complications and systemic complications. Local determinants are centered on peri/pancreatic necrosis and this could be absent, sterile or infected. Systemic determinants are centered on organ failure and this could be absent, transient or persistent. There is also a strong evidence base for the interaction between these local or systemic determinants. The determinants-based classification comprising four categories of severity is directly derived from the identification of the actual determinants of severity and their interaction as demonstrated in Table 1 [1,29-31].

The literature is replete with countless studies investigating risk factors, prognostic factors, predictors of severity and markers of severity that are based on a bewildering array (confusing and difficult to understand or to make a decision about) of underlying pathophysiologic processes in AP. And these studies often demonstrate a statistically significant association between a factor and the severity of AP. It is important to note that there are several different explanations for such an association, including five aspects; chance, bias, confounding, effect-cause and cause-effect relationships. The first four of these are non-causal associations, and only the last, the cause-effect relationship, is a causal association. In other words, when seeking the factors on which to base severity classification, it is crucial to uniquely use those having a causal association with severity, as termed 'determinant' in clinical epidemiology. There are two non-causal associations illustrating the common error used as the basis of severity assessment. Confounding occurs when the association between two variables (an exposure and an outcome) is due to a third variable (the confounder). And the important conditions are that the confounder must be causally related to the outcome and the confounder must be associated with the exposure. There are numerous examples in the AP literature where an association due to confounding is taken to be causal.

An example of confounding would be when patients with extensive pancreatic necrosis are more prone to die. This is a true non causal association as a third factor, namely infection of the necrosis, is associated with the extent of necrosis and is the cause of mortality (Figure 1A). Similarly, it is often implied that SIRS is causally associated with mortality in AP with a third factor that is organ failure being the cause of mortality in AP (Figure 1B) [1,31-33].

The same applies to all other treatments, including the need for surgery, parenteral narcotics, intravenous antibiotics, and

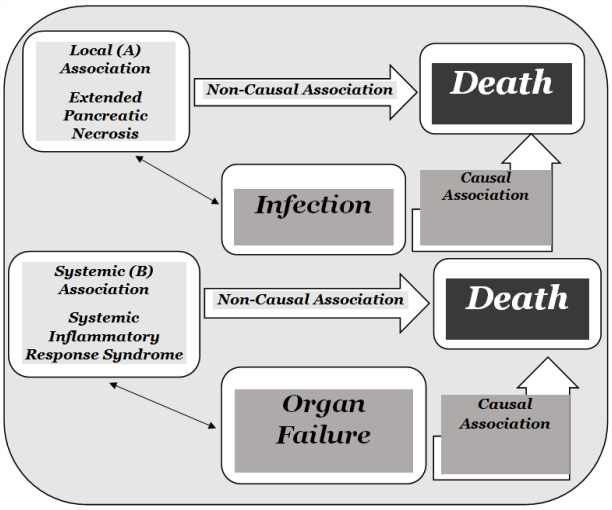

Figure 1: Local (A) and systemic (B) causal and non-causal associations in acute pancreatitis.

percutaneous drainage. This interaction is best understood as 'effect modification', which is when the effect of one determinant on an outcome varies by the presence or absence of another determinant. Thus the effect of pancreatic infection on the severity of AP depends on whether organ failure is present or not, and *vice versa*. Literature has demonstrated that mortality of AP doubles when pancreatic infection and organ failure are both present, when compared with groups of patients with either pancreatic infection or organ failure [1,31,34-38].

Diagnosis of severe acute pancreatitis complicated with intra-abdominal hypertension and abdominal compartment syndrome: The elevation of Intra-Abdominal Pressure (IAP) induced by SAP can eventually lead to Intra-Abdominal Hypertension/Abdominal Compartment Syndrome (IAH/ACS), which causes organ damage or failure. IAP is measured and monitored through the bladder. IAH (defined as continuous or repeated IAP pathologically elevates ≥ 16 cmH_2O with no organ dysfunction) is divided into four grades. ACS is defined by the persistent IAP ≥ 26.6 cmH_2O, and the existence of recent organ dysfunction and failure [1,39].

Identification of concurrent infections: The pancreatic or abdominal infection is commonly secondary to SAP. Biliary-related SAP should pay attention to the presence of biliary tract infection, showing apathy, fever, cold or chills, jaundice, sweating, tachycardia, tachypnea, leukocytosis or below the normal lower limit with left nucleus shift, and PCT elevation. In the CT images, the increased pancreatic necrosis liquefaction area and peripancreatic effusion, or the accumulated gas in the area of pancreatic necrosis, and the aggravated inflammatory response of surrounding tissues are the manifestations of infection. In such situation, positive fluid resuscitation cannot maintain vital signs or organ functions, which also marks existence of infection. Bacteria can be detected by B-ultrasound or CT-guided percutaneous fine needle aspirate, as well as abdominal cavity puncture, blood, and the first surgical specimens. There are predisposing factors of secondary infection where broad-spectrum antibiotics should be considered. When patients have a high fever, conscious changes, blurred vision, or unexplained hemobilia, deep fungal infections should be considered [18,23,24].

Diagnosis, dynamic assessment, and monitoring of organ dysfunction: SAP is prone to concurrent extra-pancreatic organ function damage such as respiration, kidney, and cardiovascular function, and further deteriorates into two or more organs dysfunction or even failure simultaneously or sequentially. In clinical practice, organ dysfunction is evaluated by Mashall standard combined with "Sequential Organ Failure Assessment" (SOFA), including ARDS Berlin definition, diagnosis, monitoring and processing of Acute Kidney Injury (AKI), liver function damage, gastrointestinal dysfunction, blood system, cardiovascular system, and central nervous system injury and failure [1,40].

Pancreatitis therapies

Principles of therapy: The aim for primary therapies is to maintain vital organ function by restoring the stability of the internal environment, improving gastrointestinal motility, and inhibiting inflammatory injury, to lower the mortality rate in the early stge. In the late stage, the main goal is to restore organ function, to control infections and local complications. Meanwhile, efforts to shorten hospital stay, to lower the rate of surgery, need to ICU care, and avoid or reduce mortality are recommended [18,23,24].

Intensive monitoring: Some parameters deserved to closely observe, such as vital signs, abdominal symptoms, routine blood test, liver and renal function, blood lipid, electrolytes, arterial blood gas, respiratory function, blood oxygenation index, blood pH and acid-base balance, blood glucose, Hematocrit (HCT), blood lactic acid, hourly urine output recording, bladder pressure, stool frequency, and radiologic imaging (including ultrasonography, CT or MRI). The adjustment of the monitoring indicators and frequency is based on the treatment goals that should be 4 to 6 hourly is recommended [18,23,24].

Fluid resuscitation: In order to prevent occurrence of "Acute Lung Injury" (ALI), "Acute Kidney Injury" (AKI), "Abdominal Compartment Syndrome" (ACS), and heart failure, patients with SAP should perform a restrictive fluid resuscitation strategy, through a fluid chart documenting rates and total volume are regulated by vital signs, urine output, lactate, and HCT to ensure organ perfusion. The parameters for fluid resuscitation should be clearly defined, such as the time points of starting and ending, the types of liquid (balanced acetic acid solution is preferred), the ratio of crystals to colloids, fluid volume, and the infusion rate with close monitoring of plasma lactic acid. All infused fluids, which titrate to the endpoint, are included in the total calculation. Fluid reactivity assessment should be carried out at the bedside and to focus on hemodynamic stability targeting to slow relieve of hemodynamic disorder (to slow down heart rate and to restore the Mean Arterial Pressure (MAP) in the range between 65 mmHg to 85 mmHg.) that does not pursue fast correction of hypovolemia. Moreover, the protocol of early goal-directed therapy for sepsis is not suitable for patients with AP [1,41].

Treatment and prevention of infection: Infectious complications; pancreatic (infected and necrosis) and extra-pancreatic (e.g. bacteremia, pneumonia, urinary tract infections) are major causes for morbidity and mortality in patients with AP. Therefore, the timely management of pancreatic infection is crucial prescribing antibiotics as per the following indications: ABP, patients with SAP who deteriorate or failure to improve after seven to ten days of hospitalization, and AP accompanied with pancreatic or extra-pancreatic infected necrosis. In contrast, prescribing prophylactic antibiotics in patients with MAP and sterile necrosis as well as the prevention of fungal infections is irrational [18,23,24].

Probiotics recent guidelines advocate against the use of probiotics for severe AP. The largest double-blinded RCT, published by Besselink et al., has demonstrated that probiotic prophylaxis did not reduce the risk of infectious complications and was associated with a higher incidence of bowel ischemia and greater mortality. Recent systematic review and meta-analyses, has supported the evidence that probiotics did not reduce pancreatic infection rates, hospital length of stay or mortality rates [17,41-43].

Nutrition: It is believed that "Early Enteral Nutrition" (EEN) has been proved holding protective effect on the integrity of enteric mucosa and hence preventing bacterial translocation; decreasing infectious complications. Therefore, EEN should be recommended as soon as possible for hospitalized patients. Parenteral nutrition should be considered only when EN has failed or the requested nutritional goal has not been reached. EN cannot be administered due to increased pain, ascites or high enteral fistula output and ileus. When patients felt hungry and the symptoms of MAP/MSAP have improved, the oral feeding should be restarted. There is no need to wait the moment when the abdominal pain has resolved and pancreatic amylase level has restored into normal. Of course, oral feeding with a low-fat solid diet appears as safe as a clear liquid diet. If necessary, nasogastric delivery is recommended with no superiority of nasojejunal delivery to nasogastric one. Additionally, EN should be delayed in critical patients with uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate >500 mL/6 h, bowel ischemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access [1,44-50].

Management of IAH and ACS: The incidences of IAH and ACS of SAP are 60% to 80% and 12% to 30%, respectively, so it makes sense to avoid the sustained IAH. The use of gastrointestinal decompression, recto-anal decompression, gastrointestinal motility promoting drugs and traditional Chinese herbal medicine together with acupuncture treatment are effective in IAP control and being prophylactic to paralytic ileus as well (treated with Neostigmine on some special acupoints). Positive fluid balance after fluid resuscitation should be avoided to prevent IAH. If hemodynamics is stable, diuretics or hemofiltration is recommended to correct the positive fluid balance with fluid overload accumulation. PCD is encouraged for ascites and encapsulated effusion.

Some clinical measures (e.g. effective analgesia and sedation and to maintain a proper body position where the height of bed head is less than 30°) can effectively help improve the abdominal wall compliance to prevent ACS. In case non-operative measures failure to control IAH and to improve respiratory, renal, and cardiovascular functions, surgical decompression therapy is recommended [39].

The use of somatostatin enzyme inhibitor: AP is induced by the activation of digestive enzymes in the pancreas. However, the inhibition of pancreatic enzyme secretion is controversial as it is not clear whether pancreatic secretion continues to occur or not during the course of AP; making the routine use of somatostatin irrational, other than the growing pancreatic pseudocysts, progressive growth of WON, pancreatic leakage, and combined gastrointestinal bleeding. In contrast, the incidence of complications would be reduced by enzyme inhibitors such as Urinastatin or Gabexate [1,23].

The management of blood glucose: When SAP is complicated by hyperglycemia or with previous history of diabetes, blood glucose should be actively monitored by Hb1C, insulin, and C-peptide. In the acute inflammatory period, insulin therapy is initially preferred by following the first basic then meal time management steps. Meanwhile, the dosage is adjusted actively to control blood sugar in a safe range according to protocols [23].

The management of biliary diseases: It is meaningful to differentially diagnose ABP as gallstone is one of the most common etiologies for AP that mandates abdominal ultrasound usage to assess cholelithiasis. At the early stages, emergency surgery is not advocated to relieve biliary obstruction. However, early endoscopic therapy [therapeutic ERCP for Endoscopic Sphincterotomy (EST), nasal bile duct drainage, and elective Laparoscopic Cholecystectomy (LC)] has become the first line to manage ABP [1,17,51-53].

As per condition; when common bile duct stones are highly suspected, MRCP or endoscopic ultrasonography should be performed, when AP combines concurrent acute cholangitis, ERCP should be implemented within 24 h of admission and when the common bile duct stones cause obstruction with no remission after medical treatment, ERCP should be implemented within seventy two hours of admission. In order to prevent necrotizing ABP from infection, postoperative cholecystectomy should be postponed until active inflammation has been relieved and fluid accumulation has disappeared or stabilized. It is cautious to screen the high-risk patients with AP after ERCP. By temporarily indwelling pancreatic duct stent and/or giving non-steroidal anti-inflammatory drug suppositories per rectum before the procedure, it should be utilized to lower the risk of severe post-ERCP pancreatitis. ERCP is not recommended if ABP has no progressive biliary obstruction and in case of non-biliary SAP [1,15,53-56].

Surgical indications and PCD: Open surgical debridement has been long suspected to increase morbidity and mortality that has encouraged to perform PCD or minimally invasive treatment initially and open surgery lately. In the early stage, when severe ACS or persistent organ failure cannot be relieved for more than two weeks, or patient has a large volume ascites with obvious symptoms of infection, or uncontrollable ascites *via* active nonsurgical treatment, or systemic symptoms or local signs are not improved or aggravated after two to three days ICU management, or the shock or vital organ dysfunction cannot be corrected, regular surgery is recommended. In the late stage (four weeks later), the surgical indicators contain the infected WON, peripancreatic or peritoneal infection, the growing pancreatic pseudocyst, and WON with pressing adjacent organs [1,21,57].

It is recommended to use a stepwise treatment protocol with minimally invasive and late laparotomy. When pseudocysts and WON further develop infections, abscesses, ruptures, and hemorrhages, it is time to commence drainage, endoscopy, or surgery. For example, with progressive enlargement of pseudocysts or symptoms of digestive tract compression, drainage is suggested to carry on. Asymptomatic WON does not mandate intervention, which may resolve spontaneously over time regardless of the size and location. However, symptomatic WON, which generally results in oppression or infection, requires intervention by drainage combined with necessary necrosectomy in the late course [1,58,59].

Continuous blood purification treatment (CBP): Improvement in several clinical outcomes, including APACHE II, serum amylase, serum Creatinine, ICU length of stay and mortality were recorded

in Severe Acute Pancreatitis (SAP) patients who underwent CBP treatment. Thus, we conclude that the CBP approach is a safe and effective treatment option for patients suffering from SAP. There is a great need for more Randomized Controlled Trials (RCTs) to confirm these advantages. In addition, future studies will be required to further define the optimal time interval and techniques for CBP commencement [1,60].

Management of etiology to prevent pancreatitis recurrence: The most common types of AP are biliary pancreatitis and alcoholic pancreatitis. ABP can be caused by gallstones, biliary infection, acute or chronic cholecystitis, biliary tract tumors, biliary tract structural abnormalities, biliary cysts, biliary ascariasis, and so on. The common treatment choice is ERCP or cholecystectomy. Primary and secondary hypertriglyceridemia can also induce AP, mandating the use of lipid-lowering agents to reduce the blood lipid levels below 5.65 mmol/L, to be reevaluated routinely after the discharge. The incidence of AP in diabetic patients is higher than that of non diabetic patients, as well as the disease severity and length of hospital stay [57,61,62].

Alcohol-induced pancreatitis often manifests as a variable spectrum, ranging from discrete episodes of AP to chronic irreversible silent changes. Therefore, patients with AP should take temperance for life. Smoking and drinking are common risk factors for AP. Smoking induces chronic inflammation of pancreas along with alcohol, high-fat diet, and other factors, especially the smoking history for more than 20 years. Even if quitting smoking, the influence would continue about 20 years. Smoking and drinking are common risk factors for AP and Chronic Pancreatitis (CP), and related to pancreatic calcification as well. Alcohol makes cigarette smoking a stronger risk factor and turns AP to be chronic. Other factors, such as obesity, pregnancy, and drugs, are all risk factors related to AP occurrence [63-67].

Sedation and analgesia: Sedation and analgesia can take effect to eliminate pain, reduce anxiety and restlessness, help antagonize the inflammatory response, and improve the patient's abdominal wall compliance to prevent ACS in patients with AP. Analgesics may be administered epidural, percutaneous, per rectum, but there is a lack of the prioritized analgesics and dosing protocol to be recommended. So, we recommend that patients with SAP within 24 h of hospital admission should receive some degrees of analgesic treatment. Moreover, Chinese medicine with electroacupuncture is also good for analgesia and sedation [68-70].

Management of complications: Local complications of AP include Acute Peripancreatic Fluid Collection (APFC), Acute Necrotic Collection (ANC), pancreatic pseudocyst, and WON. APFC and ANC would occur in the early stage. A pseudocyst will be formed four weeks later without remission of APFC. If there is obstructive oppression, bleeding, or infection complications, intervention is indicated. During the course waiting for the progression to WON (sterile or infected), if organ dysfunction continues or new organ involvement, infection or sepsis merge, or necrosis combine with hemorrhage or obstruction, it is indicated to intervene surgically [19].

The intervention, which carries on a step-up strategy including PCD, trans-gastric puncture drainage, and necrotic tissue removal, should be delayed as possible after 4 weeks of the disease onset. MRCP is the best method to diagnose pancreatic leakage through the pancreatic duct, mostly could be treated conservatively. Intervention treatment is only indicated for failed management of pancreatic leakage, pancreatic ascites, pancreatic pleural effusion, high flow pancreatic fistula, and soon after the non-operative treatment. During the AP, vascular complications such as splenic vein thrombosis, pancreatic portal hypertension, pseudo-aneurysm, arterial hemorrhage should be routinely examined, diagnosed, and correspondingly treated. At the same time, when complications of jaundice and export disorders occur during the course of AP, they should be actively managed [32].

Treatment of systemic complications: AP is often accompanied by sepsis, so it ought to take positive comprehensive treatment, like anti-infective, fluid resuscitation, maintaining organ function, and to monitor blood lactic acid and lactic acid clearance rate after the sepsis occurred. When combining the appropriate fluid resuscitation and gastrointestinal decompression, necessary thoracic puncture drainage, and mechanical respiration support with Acute Lung Injury/ Acute Respiratory Distress Syndrome (ALI / ARDS) or AKI, timely and necessary Continuous Renal Replacement Therapy (CRRT) treatment would be the optional choices, but the bedside dialysis or hemofiltration treatment cannot easily be used. Combined with acute liver function damage, treatment for normalizing gallbladder to cure jaundice or hepatoprotective treatment would be adopted according to the condition. In combination with acute heart injury, brain injury, and coagulation dysfunction, it should actively treat the primary disease of SAP, reduce inflammatory reactions, and deal with the symptoms. In severe cases, it is necessary to transfer to the ICU to strengthen intensive care and treatment [1,71-75].

Psychiatric support and psychotherapy: The treatment environment should be quiet and comfortable. Doctors should communicate fully with the patients and make necessary explanations and help them eliminate fear and build confidence to overcome the disease on the basis of necessary effective analgesia and sedation [6].

Essentials of integrative management: A large loss of body fluid to the third space is caused by the inflammatory exudation of AP, resulting in shock because of insufficient circulating blood volume or infection of the biliary tract and abdominal cavity.

Acute Gastrointestinal Injury (AGI), caused by SAP, is manifested as gastrointestinal dysfunction, gastrointestinal mucosal injury, intestinal edema, hemorrhage, paralytic ileus, and fat infiltration around the superior mesenteric artery. However, the AGI is the source and trigger that the injuries of external organs such as heart, lung, and brain are induced by SAP. In recent years, it has been found that the damage of the gastrointestinal tract barrier in SAP plays a key role in their pathophysiology process, which could induce IAH, ACS, intestinal bacterial translocation and intestinal endotoxemia, or eventually Systemic Inflammatory Response Syndrome/Multiple Organ Dysfunction Syndrome (SIRS/MODS). Therefore, effectively controlling AGI is one of the key points to improve the prognosis of AP. On the basis of the treatment of inhibition of gastric acid and bleeding, promotability of gastrointestinal motility, and alleviating peripancreatic inflammatory response, traditional Chinese herbal medicine and acupuncture are recommended to promote Qi movement and activate blood circulation to remove stasis for AGI [1,76].

The role of AGI as an engine for MODS in critically ill will be blocked. The digestive function also can be restored as soon as possible, while the traditional concept of pancreas rest is abandoned, and the intestinal arouse is intensified to guide early oral refeeding. Early prevention and treatment of organ function damage/failure

based on lung and large intestine being interior-exteriorly related AGI, induced by AP, is the engine of MODS, which results in the damage of respiratory system, kidney, heart, and brain. All organ injuries can be reinforced each other, and a vicious circle will be formed to affect the progress of the disease. The overall mortality rate is above 20%. However, the mortality rate can be as high as 35% to 50% in the first week, due to the injury or failure of single or multiple organs. Hence, while the inflammatory response is actively regulated, and the organ function is effectively supported, Chinese herbal medicine is served to treat AGI for relieving ACS. Meanwhile, new organ damage or the improvement of original organ damage can be prevented. The occurrence of MODS and the early mortality rate can be reduced ultimately, and the ventilator can be removed as soon as possible [1,76].

Prevention of infection by clearing heat and detoxifying: In the early stage, it is crucial to exert a correct fluid resuscitation protocol, improve gastrointestinal motility, and prevent bacterial translocation. In the later stage, the treatments of pancreatic necrosis, fluid collection, pseudocyst, or WON are paid more attention. If necessary, PCD or surgical drainage can be properly carried on, and activating blood and promoting water are also recommended. Infection is the main cause of high mortality in the late stage of SAP. Minimizing invasive interventions, removing tubes of invasive interventions, and transferring patients out of the ICU as soon as possible are used to reduce the incidence rate of infection. Strengthening infection surveillance includes timely collecting specimens of suspected infected patients for bacterial culture to actively obtain the drug-sensitive results, which help to guide antibiotic selection [77].

Activating blood and removing stasis to prevent and treat the late stage complications and reduce the rate of surgery, meanwhile, treatments like clearing heat and detoxifying, activating blood and removing stasis, are used to synergistically reduce the incidence of infection and the late mortality rate. In the late stage of SAP, ileus is caused by pseudocysts, WON, Infected Pancreatic Necrosis (IPN), hemorrhage, pancreatic portal hypertension, gastric outlet disorders, inflammatory adhesive intestinal obstruction, or intestinal obstruction. Not only the patient's life quality after discharge is affected, but the severe lesions could also occur, which result in an increasing surgical rate and mortality. Therefore, according to different complications and their causes, targeted syndrome differentiation and treatment is recommended to carry out to reduce the operation rate and improve the prognosis [77,78].

Conclusions

Strengthening the etiologic management of AP to preventively treat disease

The recurrence of AP, the family, and socioeconomic burden can be effectively reduced by strengthening the etiologic management. Combined with the specific etiology of the patient, health education and necessary interventions before discharge are recommended, including quitting smoking and drinking, changing dietary habits and structure, monitoring and controlling blood lipid and blood sugar, controlling weight, preventing biliary stones, and insisting on long-term outpatient follow-up or APP automatic follow-up review.

Efficacy assessment criteria

The evaluation criteria of the efficacy of AP treatment include evaluation criterion of clinical symptoms and signs, efficacy evaluation of serum pancreatic enzymes, efficacy evaluation of imaging, evaluation criteria of pancreatic endocrine and exocrine functions, and evaluation of life quality.

Up to now, the main endpoints of efficacy evaluation criteria have been adopted in most international clinical trials, including case fatality rate, complication rate (fluid collection, WON, IPN, and hemorrhage), surgical rate, and length of stay.

Assessment criteria: Clinical symptoms and signs

Patients with AP have abdominal pain and abdominal distension as the main symptoms, with common signs such as abdominal tenderness, rebound tenderness, and muscle tension. The grading is determined by changes in symptoms and signs at the time of admission and before discharge. Clinical recovery: Main symptoms and signs have disappeared. Markedly effective: Significant improvement in the main symptoms and signs, without affecting the patient's appetite and rest. Effective: Significant improvement in major symptoms and signs, with minor influence on patients' appetite and rest. Ineffective: No significant improvement in main symptoms and signs, or even aggravation.

The degree evaluation of abdominal pain and abdominal distension

As to comprehensive assessment of efficacy, abdominal pain is the main symptom and abdominal distension is the secondary syndrome.

The "Visual Analogue Scale" (VAS) method is used to record the degree of abdominal pain and abdominal distension, which depend on the subjective symptom grading of patients. On the basis of 100 mm vertical scale, the 0 mm is defined as the minimum with no pain or abdominal distension, and the 100 mm is defined as the maximum and unbearable pain or abdominal distension. Patients are requested to make a mark on the scale, which can reflect the levels of their pain and abdominal distension. The VAS method is used to score the degree of pain and abdominal distention, separately on the 0^{th}, 2^{nd}, 5^{th}, 7^{th}, and 14^{th} days. The efficacy is judged by using the Nimodipine method and the following criteria.

Assessment criteria: Laboratory test results

Clinical recovery: Pancreatic enzymology, liver and renal function, blood lipid, blood glucose, and routine blood test have returned to normal.

Markedly effective: Pancreatic enzymology has returned to normal, but liver and renal function, blood lipid, blood glucose, and routine blood test have not fully returned to normal.

Effective: Pancreatic enzymology has significantly reduced, but liver and renal function, blood lipid, blood glucose, and routine blood test are not all normal.

Ineffective: Pancreatic enzymology, liver and renal function, blood lipid, blood glucose, and routine blood test have not returned to normal.

Assessment criteria: Pancreatic imaging evaluation index

The pancreatic and surrounding lesions are recommended to be used as evaluation indicators.

Clinical recovery: The pancreatic morphology and parenchyma have returned to normal without effusion, edema, pseudocyst, or enveloping necrosis.

Markedly effective: The pancreatic morphology and parenchyma have not returned to normal, but abdominal pain and abdominal

Table 1: Determinants-based classification of acute pancreatitis severity.

Severity Determinants ➡ / Severity Category ⬇	Local Determinants ± Systemic Determinants
Mild	No peri/pancreatic necrosis **And** No organ failure
	No *local **Or** **systemic complications
***Moderate	Sterile peri/pancreatic necrosis **Or** Transient organ failure (<48 Hours)
***Severe	Infected peri/pancreatic necrosis **Or** Persistent single organ failure (>48 Hours)
Critically Infected	Peri/pancreatic necrosis **And** Persistent multiple organ failure (>48 Hours)

*Local complications: pancreatic or peripancreatic fluid collections, splenic and portal vein thrombosis, intestinal ischemia and gastric outlet dysfunction
**Systemic complications: exacerbation of pre-existing comorbidity
*** Severity is graded on the basis of more severe local or systemic determinant factor

Table 2: Updated knowledge related to epidemiology, evaluation, and management of acute pancreatitis.

Category	Factor
EPIDEMIOLOGY	1. Globally the incidence of AP is increasing, but mortality is decreasing.
	2. Alcohol and gallstones remain the most common etiologies for AP.
	3. Smoking is an independent risk factor for pancreatitis.
	4. Cannabis is a possible risk factor for toxin-induced AP.
	5. Conjugant with inflammatory bowel disease, AP is typically due to gallstones or medications.
	6. Conjugant with severe renal disease, risk of AP is higher with ongoing peritoneal dialysis.
	7. Conjugant with pancreatic cancer is uncommon but established cause of first-attack pancreatitis.
	8. The risk of AP and severe AP appears to increase in proportion to triglyceride value.
EVALUATION	1. Cross-sectional imaging remains over-utilized during the initial evaluation of AP.
	2. Risk stratification tools have moderate predictive value for SAP.
MANAGEMENT	1. Goal-directed Fluid Therapy (FT) is recommended as early treatment of AP.
	2. Recommended FT fluids are normal saline or lactated Ringer's.
	3. Early oral feeding is recommended, beginning within 24 hours, for MAP.
	4. Enteral nutritional support is favored over parental nutrition in SAP.
	5. Prophylactic antibiotics are not recommended for NAP.
	6. Probiotics are not recommended for SAP.
	7. Urgent ERCP within 24 hours for ABP complicated by cholangitis.
	8. Routine use of urgent ERCP is not recommended for ABP.
	9. Recommended same-hospitalization and alcohol cessation counseling for alcohol-induced AP.
	10. Recommended same-admission cholecystectomy for mild ABP.
	21. Rectal indomethacin and peri-procedural FT each reduce post-ERCP pancreatitis.

distension cannot exist with no influence on the patient's appetite and rest.

Effective: The pancreatic morphology and parenchyma have not returned to normal, but abdominal pain and abdominal distension can exist affecting the patient's appetite and rest.

Ineffective: The pancreatic morphology and parenchyma have not returned to normal, but abdominal pain and abdominal distension can exist, even the patient cannot normally feed and rest.

Treatment algorithm for AP

Diagnosis (at least two criteria): (1) Upper abdominal pain (2) Serum amylase or lipase (or both) >3 times the upper normal limit (3) Typical findings on imaging.

Revealing etiology:

- Medical history
- Family history
- Medication and alcohol use
- Laboratory tests (liver enzymes, triglycerides, calcium)
- Transabdominal ultrasound.

Initial treatment:

- Goal-directed fluid resuscitation with Ringer's lactate solution
- Nutritional support after 72 h
- ERCP in cases of cholangitis or persistent cholestasis
- No role for prophylactic antibiotics or probiotics
- Maximal supportive care on ICU in cases of organ failure.

Treatment of necrotizing pancreatitis:

- Minimally invasive step-up approach in cases of proven or highly suspected infected necrotizing pancreatitis
- Intervention preferably delayed until the phase of walled-off necrosis
- Assess for disrupted or disconnected pancreatic duct following

necrotizing pancreatitis.

Prevention of recurrence:

- (Presumed) idiopathic pancreatitis:
- Repeat abdominal ultrasound
- Endoscopic ultrasound
- Mild biliary pancreatitis: Cholecystectomy during admission
- Severe biliary pancreatitis: Cholecystectomy after 6 weeks.
- As a conclusion summary from this review; it seems that AP clinical assessment, prediction of prognosis and finally management therapies seem to be inaccurate, delayed and this in turn would increase disease morbidity and mortality. Dependently, suggesting application of upmost best updated clinical practices holds rationale of documented evidence. Table 2, gathers updated knowledge related to epidemiology, evaluation and management of AP.

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