Open Access

OBM Hepatology and Gastroenterology

LIDSEN Publishing Inc.

Review

Review of Current Evidence in Acute Pancreatitis

Samantha Varley [1, †, *], Kirsten Rossi [2, †], Meghan Murray [2, †], Alissa Nichole [1, †]

1. Department of Gastroenterology, University Hospital of Udine, Udine, Italy; E-Mails: samanthavarley@hotmail.com; alissanicholern@gmail.com
2. Department of Medicine, University Hospital of Udine, Udine, Italy; E-Mails: kdeeko@outlook.com; meghanmurray84@hotmail.com

† These authors contributed equally to this work.

* **Correspondence:** Samantha Varley; E-Mail: samanthavarley@hotmail.com

Academic Editor: Prashanth Rawla

Special Issue: Pancreatitis: New Insights into Etiology, Pathogenesis, Diagnosis, Management and Complications

OBM Hepatology and Gastroenterology
2019, volume 3, issue 3
doi:10.21926/obm.hg.1903026

Received: May 17, 2019
Accepted: July 05, 2019
Published: July 12, 2019

Abstract

Acute pancreatitis (AP), an inflammatory condition of the pancreas, is one of the most common ailments of the gastrointestinal system, which results in significant morbidity and mortality. The main etiological causes of AP include alcohol consumption, gallstones, hypertriglyceridemia, and biliary stones. The clinical signs and symptoms of AP and the diagnostic criteria for this disease have been well established. Multiple scoring systems are applied to predict the severity and prognosis of AP, and the associated mortality. The present review of the literature highlights the recent significant contributions in the areas of etiology, risk factors, epidemiology, diagnosis, complications, prognosis, and the latest modalities in the treatment, which could be beneficial in the management of AP.

Keywords

Pancreatitis; epidemiology; diagnosis; complications; treatment; prognosis

© 2019 by the author. This is an open access article distributed under the conditions of the Creative Commons by Attribution License, which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

1. Introduction

Acute pancreatitis (AP) develops as a result of premature activation of digestive enzymes released by the exocrine pancreas, mainly the conversion of trypsinogen into trypsin, inside the acinar cells, leading to the self-digestion of these cells and the stimulation of macrophages. The stimulation of macrophages, in turn, induces the production of pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), and interleukins (IL), all of which play a vital role in the pathogenesis of AP [1, 2]. The majority of the cases of AP are mild (80%), while a small number of cases are severe in nature with a mortality rate of up to 50%; these severe cases serve as the key to understand the etiology, pathology, severity, prognosis, and complications associated with AP, so as to provide adequate and timely management of the disease [3, 4]. In this compilation and review, it may be observed that, for decades, a considerable amount of controversy has been existing regarding two aspects which are fundamental and critical to this subject. The first aspect is the practical application of the standardized universal criteria of severity and prognosis in AP. The second aspect is the management of fluid resuscitation and the role of early nutrition in AP. The accumulation of expert opinions resulting in a consensus has been able to elucidate most of the guidelines for the diagnosis, criteria, and management of AP. Recent research has resulted in novel advances with positive impacts such as a reduction in hospital stay, morbidity, and mortality associated with AP. The present review of the literature highlights the recent significant contributions in the areas of etiology, risk factors, epidemiology, diagnosis, complications, prognosis, and the latest modalities in treatment which could prove to be advantageous in the management of AP [5-7].

2. Etiology

Gallstones occupy the first and the most important position in the list of causes of AP (40%), and are more prevalent in women [8]. When migrating in nature, gallstones may obstruct the pancreatic duct, a mechanism shared with endoscopic retrograde cholangiopancreatography (ERCP) (5%–10%), pancreas divisum, and dysfunction of the sphincter of Oddi [9]. Prolonged consumption of alcohol (4–6 drinks/day for >5 years) is the second important cause of AP (30%), and causes the disease by lowering the activation threshold of trypsin enzyme, resulting in cell necrosis [2]. This mechanism is observed more frequently in men, probably due to the differences in the intake or in genetics. The type of alcohol ingested and the excessive consumption of alcohol although not for long-term do not present a risk of developing AP. The mechanisms underlying the causes of AP or CP (chronic pancreatitis) include direct toxicity and immunological mechanisms [10, 11]. Hypertriglyceridemia occupies the third position among the causes of AP (2%–5%) in the absence of other etiological factors, with a risk factor of 1.5%, and when the levels are >1000 mg/dL, the risk increases to 20.2%. Type I, IV, and V dyslipidemia have also been reported to be associated with AP (Frederickson Classification) [12].

Smoking has been reported to be associated with 50% of the cases of AP [13, 14]. Active smokers are at 20% more risk of suffering from the pancreatic disease compared to ex-smokers [15]. The harmful and carcinogenic effects of smoking along with its high global prevalence have

caused it to be the most important modifiable risk factor for AP [16, 17]. Drugs cause less than 5% of cases of AP, mostly mild AP. Among the AP-causing drugs are azathioprine, didanosine, estrogen, furosemide, pentamidine, sulfonamides, tetracycline, valproic acid, 6-mercaptopurine, angiotensin-converting enzyme inhibitors, and mesalamine [18, 19].

Mutations and polymorphisms in certain genes, including those encoding cationic trypsinogen, serine protease inhibitor of Kazal type 1, a regulator of transmembrane conductance in cystic fibrosis, chymotrypsin C, calcium-sensitive receptor, and claudin-2, have been reported to be associated with AP and CP. These serve as cofactors interacting with other causes, for example, the mutation of claudin-2 in synergism with alcohol consumption [2, 10, 20].

Other potential factors resulting in AP include genetic polymorphisms, smoking, environmental toxins, and the effects of associated comorbidities, obesity, and Type 2 Diabetes (DM2) [21, 22]. Autoimmune causes are present in less than 1% of the cases [23, 24]. There are two types of autoimmune causes for AP: The type 1 which affects pancreas, kidneys, and salivary glands, and causes obstructive jaundice with mild elevation in the levels of the immunoglobulin G4; and the type 2 which affects only pancreas, occurs in young patients, and does not elevate the levels of immunoglobulin G4. Both types of causes respond to treatment with glucocorticoids [25-27].

Penetrating abdominal traumas, particularly those of the spine, result in the development of AP in 1% of the cases [28]. Infectious causes (cytomegalovirus, mumps virus, and Epstein-Barr virus) and parasites (such as Ascaris and Taenia) cause 1% or more of the cases [29]. Obesity has been well-established as a risk factor for AP, and the risk is more severe in cases with central obesity. DM2 has been reported to cause an increase of 2–3 times in the risk of developing AP. Cirrhosis doubles the mortality in AP [30, 31]. AP has also been associated with the time and duration of stress which may be beneficial or harmful to the exocrine pancreas. Acute short-term stress may be useful for high-risk procedures, such as ERCP, while chronic stress may be harmful [32].

3. Epidemiology

AP is one of the most common gastrointestinal disorders which require hospitalization. Its annual incidence is 13 to 45 per 100,000 people [33, 34]. Most of the cases are mild and self-limited, 30% of the cases are moderately severe, and only 10% of the cases are severe. Organic failure is the main determinant of the seriousness of the disease and the cause of early death. The overall mortality in AP is 3%–6%, which increases to 30% in case of severe AP, mainly due to secondary infections, including the infected acute necrotizing pancreatitis (PAN) and sepsis, being responsible for an increasing number of deaths in recent years [4].

4. Diagnosis

The diagnosis of AP is based on two or more of the following criteria: characteristic abdominal pain, elevated levels of serum lipase and amylase [at least three times of the normal value], and/or findings in the images of abdomen, including the ultrasound (USG) images, computed tomography (CT) scans, or magnetic resonance imaging (MRI) [6, 35].

4.1 Clinical History and Physical Examination

Abdominal pain in the upper left quadrant of the periumbilical region and/or epigastrium usually appears suddenly. Such pain may be generalized and may radiate to the thorax and middle back. This pain usually begins after the ingestion of fatty food or alcohol. The pain is often associated with nausea and vomiting, fullness, abdominal distension, hiccups, indigestion, and oliguria [36]. The physical manifestations are variable and may include fever, hypotension, tachycardia, tachypnea, jaundice, diaphoresis, and alteration in the state of consciousness. There may also be signs of abdominal guarding and palpation and even peritoneal irritation. Cullen's sign (ecchymosis and edema of the subcutaneous tissue) and Gray Turner's sign (ecchymosis of the flanks) have been reported to be associated with severe AP, and denote poor prognosis [37]. Therefore, it is important to obtain detailed information regarding the patient's history of previous AP, gallstones, alcohol and drug consumption, hyperlipidemia, trauma or recent invasive abdominal procedures, and family history of any pancreatic disease.

4.2 Laboratory Tests

Laboratory examination includes complete blood counts, metabolic panel (triglycerides, renal function, and hepatic function), levels of lipase, amylase, lactate dehydrogenase, calcium, magnesium, and phosphorus (in case of a history of alcohol abuse), and urine analysis [38]. In order to develop the clinical profile, tests for C-Reactive Protein (CRP), arterial blood gases, and levels of IL-6 or IL-8 are performed [39]. The levels of Lipase are more sensitive and specific in comparison to the levels of amylase. Hyperamylasemia may occur as a result of renal failure, parotitis, ischemia, and intestinal obstruction, macroamylasemia, and the use of multiple medications. The lipase levels may increase spontaneously in bacterial peritonitis, intestinal ischemia, and esophagitis [40].

4.3 Imaging Tests

The guidelines provided by the American College of Gastroenterology (ACG) recommend that abdominal ultrasound (USG) must be performed for all patients with suspected AP. Abdominal USG is useful for the diagnosis of biliary AP, although its usefulness becomes limited in the presence of superimposed intestinal gas and choledocholithiasis, and it is not useful in evaluating prognosis [41]. Computed tomography (CT) is the standard diagnostic method used for the prediction and evaluation of the prognosis of AP severity. CT is also the diagnostic test of choice for differential diagnosis in the patients with severe abdominal pain that mimics AP or the patients with atypical symptoms and mild elevations in the serum levels of pancreatic enzymes, as well as in cases of conservative therapeutic failure or in the context of clinical deterioration. The optimal time to perform CT is 72–96 h after the onset of symptoms [42]. Magnetic resonance imaging (MRI) is useful in cases of hypersensitivity as it provides a contrast medium and exhibits advantage over CT by enabling the evaluation of the main pancreatic duct and the presence of collections [43]. Endoscopic retrograde cholangiopancreatography (ERCP) is used in cases of choledocholithiasis, and is similar to magnetic resonance (MR) cholangiopancreatography, which is a non-invasive method that does not require the use of gadolinium [13].

5. Types and Phases

There are two types of AP:

Interstitial Edematous AP: This type of AP occurs in 80%–90% of the cases. It involves acute inflammation of the pancreatic parenchyma and/or peripancreatic tissue without necrosis, which is detectable in CT. The illness resolves in the first week.

Necrotizing AP: This type of AP involves inflammation associated with pancreatic or peripancreatic necrosis, which is detectable in CT. This is the most aggressive form of AP [44–46].

Necrotizing AP comprises two phases which can be overcome. One is the early phase that remits in one week, and may extend to two weeks. This phase is characterized by systemic inflammatory response syndrome (SIRS) and/or organ failure. The other phase is the late phase that lasts for weeks or months, and is characterized by symptoms of systemic inflammation, local and systemic complications, and/or persistent organ failure [45, 46].

6. Degrees of Severity

It is important to define and stratify AP in order to: a) Identify potentially serious patients who require aggressive treatment right at the time of admission, b) Identify the patients that merit referral for specialized care, and c) Stratify the AP patients into subgroups in case of persistent organ failure and other complications including both local or systemic ones.

6.1 The Atlanta Classification of AP

Mild AP: Absence of organ failure and local or systemic complications; resolves within one week; does not usually require imaging examinations; and mortality is rare.

Moderately Severe AP: The presence of transient organ failure or local or systemic complications; may resolve in the first 48 h (transient organ failure or acute liquid collection) without intervention or may require prolonged specialized attention (sterile PAN without organ failure) resolving in 2–3 weeks, with morbidity and mortality rates <8%.

Severe AP: The presence of persistent organ failure (single or multiple) along with one or more local or systemic complications; may occur in the early phase (with a mortality rate of 36%–50%) or in the late phase [45-47].

6.2 Prediction of Severity and Forecast

The identification of severity upon admission is essential for a) determining if the patient requires to enter intermediate care or intensive care, b) undertaking decisions regarding the initiation of effective and timely therapy, and c) assessing the risk of morbidity and mortality [48]. Severity is established at the time of admission and at 48 h post admission, by assessing the combination of the following parameters:

Clinical Parameters: Age ≥ 60 years, pre-existing disease (a score of ≥2 in the Charlson comorbidity index), obesity (BMI > 30), and prolonged consumption of alcohol increase the risk of complications or death [36].

Laboratory Studies: Hemoconcentration and azotemia, or alteration in the levels of inflammatory markers (CRP > 150 mg/L, and levels of IL-6, IL-8, and IL-10) quantify the decrease in

the intravascular volume for losses in the third space [40, 49]. If the blood urea nitrogen (BUN), creatinine, and elevated hematocrit are not restored to normal range even after an aggressive resuscitation with fluids, then these are considered predictors of severe AP. The levels of amylase and lipase do not serve as the predictors of the severity of AP [40, 50]. Serum biomarkers such as the activation peptide of urinary trypsin and serum amyloid A have been reported as the early predictors of AP severity [50].

6.3 Systemic Inflammatory Response Syndrome (SIRS)

SIRS is characterized by the presence of more than two of the following: Temperature < 36 ℃ or > 38 ℃, heart rate > 90/min, respiratory rate > 20/min, and white blood cell count < 4000 or > 12000/mm^3. SIRS predicts the AP severity at the time of admission and at 48 h post entry. In predicting mortality, it exhibits a sensitivity of 77%–89% and a specificity of 79%–86% [51]. Persistent SIRS in association with multiple organ failure results in 25% mortality, compared to transient SIRS which results in 8% mortality [52].

6.4 Scoring Systems

a) Ranson criteria: With 80% sensitivity in the first 48 h. Values of 11 factors (5 on admission and 6 at 48 h) and a value of ≥ 3 points is considered severe AP [53, 54].

b) APACHE II and APACHE-O: APACHE II exhibits a sensitivity of 95% when used daily with the patients in intensive care. It assesses 12 criteria, and a score ≥ 8 is considered a risk of death, with the risk increasing as the score increases. APACHE-O is used when the obesity factor is added to the score [55-58].

c) Modified Glasgow Criteria (Imrie): It has a sensitivity of 80% when used in the first 48 h, and a value ≥ 3 signifies severe AP [59, 60].

d) BALI score: It evaluates four variables, BUN ≥ 25 mg/dL, age ≥ 65 years, LDH ≥ 300 U/L, and IL-6 ≥ 300 pg/mL, at admission and at 48 h. Three positive variables are associated with a mortality value of ≥ 25%, while four positive variables represent mortality ≥ 50% [44].

e) PANC 3 Score: This is extremely useful due to its efficiency, convenience in usage, and the speed of generating results. It evaluates three variables: Hematocrit > 44 g/dL, BMI > 30 kg/m^2, and pleural effusion x-ray (the last variable being the most useful one for predicting severe AP) [61].

Recently, three scoring systems have been proposed, and each of these predicts AP severity in the first 24 h [62].

f) BISAP: It evaluates five criteria: BUN > 25 mg/dL, age > 60 years, mental deterioration, SIRS, and pleural effusion. A value > 2 signifies a 10-times increased risk of mortality.

g) HAPS: It identifies the patients who do not require intensive care and those who would probably not develop severe AP, in 24 h [61].

h) POP: It has greater sensitivity compared to APACHE II and Glasgow. It evaluates six variables: age, mean arterial pressure, arterial pH, urea, calcium, and PaO_2/FiO_2. The scores range from 0 to 40, a higher score representing higher mortality [51, 61, 63].

Other scoring systems are also available, such as:

i) Determinant-Based System: It is based on the identification of radiological changes in the collections, sterile or infected PAN, and signs of organ failure [64].

j) Severity index by CT: This one sums the Balthazar score and the degree of necrosis [54, 56, 60, 65]. It identifies the presence of peripancreatic inflammation, phlegmon, and necrosis. A total score ≥ 5 is associated with prolonged hospital stay and a 15-times increase in the morbidity and mortality in comparison to the patients with a score of <5. Exceeding Ranson's prediction of severity and that of APACHE II, it exhibits a sensitivity of 87% and a specificity value of 83%.

k) Classification of Atlanta: It is based on a multifactorial scoring system and the predictive factors of severity. In the first 24 h, it includes clinical suspicion, an increase in BMI, pleural effusion, and increased APACHE II value as factors. After 24 h, it includes persistent organ failure and/or Glasgow Imrie value > 3, and a higher severity score in case of a CRP value >150 mg/L or increased levels of biomarkers IL-1, IL-6, IL-8, IL-10, procalcitonin, and beta-receptor antagonist [45, 46, 56, 61, 66].

l) EPIC: It evaluates the presence of ascites, pleural effusion, and retroperitoneal edema, and predicts the occurrence of early organ failure with a precision similar to or greater than that of SIRS, BISAP, and Balthazar. It also predicts the duration of hospital stay. It is not useful in determining the severity of organ failure or the number of failed organs [67].

There is no reliable predictor or a consensus on the preference of use of one or the other systems in case of persistent organ failure. Despite the evidence, no studies have reported a direct relationship between prognostic and mortality markers [67]. On the basis of expert opinions, it is possible to state that despite the simplicity of Ranson's criteria, its convenience to remember, and the wide availability of tests to perform in any laboratory, this prediction rule is full of uncertainties, uncomfortable and confusing as the criteria vary according to the biliary etiology, and instead of evaluating 11 factors, it sometimes evaluates 22. All the scoring systems have their individual advantages, although with the limitation that most of these require evaluation beginning from the time of admission until 48 h only, leaving a blind period that is critical in the management and detection of complications. The APACHE II score has the advantage of allowing score calculation at admission as well as at any time point during the evolution of the condition of the patient. The APACHE II score is extremely effective in the accurate prediction of severity and prognosis of AP, and together with the CT Severity Index, provides outcomes that are superior to the numerous other methods available, this is so because it also evaluates extension and necrosis. Therefore, it may be concluded that Ranson’s Criteria does have an advantage when approaching the patient in the emergency room or at the time of admission; however, the APACHE II Score forms the basis for a constant clinical–laboratory combined monitoring [56, 57, 59, 61].

7. Treatment

In medical settings, it is essential to generate an accurate diagnosis, triage appropriately, provide high-quality supportive care, continuously monitor and treat the complications, and prevent relapse [1, 68, 69]. Mild AP may be treated on an outpatient basis with oral analgesia; however, most cases require hospitalization [68]. The first 48–72 h should be focused on detecting and monitoring the worsening blood pressure, oxygen saturation, and decreasing urine output. The presence of hypotension, tachycardia, hypoxemia, and oliguria for >48 h indicates persistent organ failure, and if the patient does not respond with adequate IV fluid therapy, management in ICU might be required which probably involves gastroenterology or general surgery [6]. The physical examination must be repeated every 4–8 h, for monitoring the alteration in the mental

state and/or abdominal stiffness which would indicate the presence of fluid in the third space or abdominal compartment syndrome [70, 71]. In the first 6–12 h, complete metabolic panel, complete blood count, serum levels of calcium, magnesium, glucose, and BUN, should be performed as required according to the patient's condition. Hypocalcemia and hypomagnesemia should be corrected intravenously. Hyperglycemia must be managed with insulin. Hemoconcentration and elevated BUN levels indicate inadequate hydration or kidney injury, which requires increasing the supply of IV fluids. Abdominal CT should be repeated if the patient responds poorly to the standard therapy in order to evaluate complications or the worsening condition [66].

7.1 Pain Control

Opioids are the analgesics of choice for AP treatment. Opioids have the advantage of decreasing the requirement for supplemental analgesia when compared with the other options, although no difference in the risk of complications or serious adverse events is there. The pain medications used in AP are as follows: buprenorphine, pethidine, pentazocine, fentanyl, and morphine [72, 73].

7.2 Resuscitation with Fluids

Substantial losses in the third space and depletion of the intravascular volume (hypovolemia) leading to hypoperfusion in the splenic bed serve as negative predictors of AP (hemoconcentration and azotemia) [74]. Retrospective studies have suggested that aggressive administration of fluids during the first 24 h reduces morbidity and mortality. Most of the currently available guidelines recommend early and vigorous administration of IV fluids, which has significance during the first 12–24 h and holds little value after this time.

Studies from the Mayo Clinic in the United States demonstrated that the above-mentioned management results in a decrease in the incidence of organ failure, the SIRS score, and the length of hospital/ICU stay [74]. American Gastroenterological Association (AGA) has recommended the administration of balanced crystalloid solution at a rate of 200–500 mL/h or at 5–10 mL/kg weight/h (i.e., 2500–4000 mL in the first 24 h) to maintain an effective mean arterial pressure (MAP) (65 mmHg) and a urinary output of 0.5 mL/kg weight/h, in order to decrease the BUN levels [5]. Ringer's lactate solution is superior to the normal saline solution, as it reduces the number of inflammatory markers (CRP) as well as the incidence of SIRS [75, 76]. An experimental study conducted on rats with PAN demonstrated the use of Ringer's ethyl pyruvate solution (replacing Lactate) to be a powerful antioxidant that decreased edema and pancreatic necrosis, achieving a reduction in consequential organ failure and improvement in survival [74].

Colloids should be considered in case of hematocrit < 25% and a value of <2 g/dL for human albumin in hypoalbuminemia [62]. The practical methods for the measurement of the adequacy of fluid therapy and that of the state of hydration are cardiopulmonary monitoring, clinical and hourly measurement of the urine output, monitoring of hematocrit (35%–44%), and the correction of BUN and creatinine, which have been demonstrated to limit necrosis. A decrease in the hematocrit levels up to 44%–47% in the first 24 h is considered a major risk factor for the development of necrosis [62]. The main risk factor for fluid restitution is the overload of volume which increases the risk of abdominal compartment syndrome, sepsis, the requirement for

intubation, and death [41, 71]. Therefore, it must be adapted according to the degree of intravascular volume depletion and the cardiopulmonary reserve, especially in patients with renal and cardiopulmonary failure [62].

7.3 Nutrition

In the last decade, nutritional support has become one of the key areas in the treatment of AP, especially in case of severe AP. There has been a focus on specialized nutrition, with a preference for enteral nutrition (EN) over the total parenteral nutrition (TPN) administered from the early form. The use of polymeric diets has been recommended, which includes three basic nutrients i.e., proteins, carbohydrates, and fats, accompanied by clear liquids. According to the European Society for Parenteral and Enteral Nutrition (ESPEN), enteral formulas containing small peptides and medium chain triglycerides should be given preference, even though polymeric formulas are equally safe. TPN is more expensive, riskier, and less effective in comparison to the EN in the AP patients, and is, therefore, reserved as the second line of treatment. In mild AP without organ failure or necrosis, EN may be commenced from the time of admission with a soft or solid diet low in fat, in the absence of intense pain, nausea, vomiting, and ileus, without waiting to achieve the normalized levels of pancreatic enzymes. This diet is safe and has been associated with a shorter hospital stay when compared to a clear liquid diet progressing gradually to a solid diet [74, 77]. In severe AP, intolerance to the oral route administration, or when the clinical signs of AP worsen with the use of EN, TPN is recommended. It has also been recommended to maintain minimum perfusion of EN in order to preserve the trophic effect of the intestinal mucosa. EN may be commenced in the first 3–5 days when there is improvement in the symptoms and the levels of the inflammatory markers, by using the nasojejunal tube (Dobhoff), which is better than the nasogastric tube as it decreases the pancreatic secretion, prevents infections and the risk of bacterial translocation from the intestine to the pancreas, decreases the requirement for surgical interventions, and is associated with short hospital/ICU stay, independent of the APACHE II score, without changes in the occurrence of complications and mortality, when compared with the TPN. A recent meta-analysis also demonstrated a reduction in the mortality and organ failure with improvement in nutrition [74, 77-79].

7.4 Antibiotics

AP is a sterile inflammation, and only one-third of the cases develop infected PAN with a significant risk of death > 50%. The use of antibiotics should be reserved for cases with suspicion or confirmation of local or extrapancreatic infections, such as pneumonia, urinary tract infection, cholangitis, sepsis, and phlebitis in a venipuncture site, or as recommended by the guidelines of AGA and ACG clinics, restricting their use to the patients with PAN with pancreatic necrosis > 30% or pancreatic necrosis or infected extrapancreatic, which should be suspected on the basis of clinical deterioration or poor patient improvement after 7–10 days of hospital treatment [41]. Antibiotics are also indicated in the case of sepsis; therefore, simultaneous PAN cultures (blood, urine, and other bodily and tracheal fluids) should be performed in order to identify etiology. Antibiotics must be administered in accordance with the sensitivity, and the duration of usage should depend on the clinical response and negativity of the cultures [80-82]. The use of prophylactic antibiotics has not been indicated in case of mild AP, and moderately severe, severe,

or sterile necrosis, as it increases the prevalence of fungal infections and the development of multidrug resistance in microorganisms [80-83].

Various meta-analyses and reviews available in Cochrane have concluded that carbapenems, especially imipenem/cilastatin, form the empiric monotherapy which is relatively more effective in the treatment of pancreatic infection. Quinolones, metronidazole, and cephalosporins used at high doses may also be effective as most of the isolated pathogens are *E. coli*, Bacteroides, Enterobacter, Klebsiella, *S. faecalis*, *S. epidermidis*, and *S. aureus* [84].

7.5 Probiotics and Prebiotics

The Dutch AP Study Group observed that the use of a probiotic cocktail increased death with high significance statistics; therefore, the use of probiotics is contra-indicated. Similar outcomes have been observed with prebiotics [85, 86].

7.6 Alternative Medicine

A review in Cochrane evaluated 15 Chinese studies, determining that the use of licorice root, ginseng, peony, and bark of Chinese cinnamon in AP reduced mortality, surgical interventions, and organ failure, although the quality of these studies was quite low [87, 88].

7.7 Other Drugs

The use of heparin (preferably the one with low molecular weight) in moderately severe to severe AP has been associated with better evolution with a lower incidence of necrosis, ability to improve pancreatic microcirculation and anti-inflammatory effect through a reduction in the stimulation of macrophages and monocytes [89]. Additionally, experimental studies have revealed that heparin reduces the levels of amylase, endothelin-1, inflammatory cytokines, and TNF-α, and causes the activation of NF-kB [12]. Simvastatin has been reported as a promising drug for the prophylaxis of new episodes in recurrent AP [12]. Various clinical trials have demonstrated the benefit of using anti-TNF-α in selected patients, as TNF-α plays a central role in the pathogenesis of local and systemic complications in PA (4). Norepinephrine, as in the patients with sepsis, is the first line vasopressor for the maintenance of MAP ≥ 65 mmHg, even when hypovolemia has not yet been treated. Continuous Hemodiafiltration (CHDF) vs. Continuous Veno-Venous Hemofiltration (CVVH) is also used in a certain patient. CHDF is used widely in Japan as a therapy for blood purification in patients with morbid conditions and is believed to prevent organ failure. The role of CHDF has been investigated using the polymethyl methacrylate (PMMA) membrane for the elimination of pro-inflammatory cytokines in severe AP. Pupelis et al., in a 10-year retrospective review of studies using CVVH in patients with AP, concluded that balancing the replacement of fluids and the elimination of blood cytokines resulted in a decrease in the requirement for surgical interventions from 41% to 19% [90, 91]. The Japanese guidelines suggest that organ failure, but not mortality, can be prevented in severe AP. Xu et al. [92] recently demonstrated a decrease in the levels of TNF-α and a positive correlation between the blood levels of TNF-α and the intra-abdominal pressure.

7.8 Heparanase Inhibitors

A clinical-biochemical model of AP induction was studied in rats with analogs of interstitial pancreatic secretagogues, specifically cerulein, which increase the expression and activity of heparanase (an endoglycoside regulator of several physiological and pathological processes, as well as angiogenesis, metastatic cancer, and inflammation). Heparanase is highly involved in AP pathogenesis, and the use of heparanase inhibitors causes a marked decrease in edema and inflammation. Currently, heparanase inhibitors are being used in phase I/II clinical trials of cancer patients, and are, therefore, expected to be beneficial in AP as well [93].

7.9 Endoscopic Treatment

ERCP along with sphincterotomy decreases mortality and complications when compared with non-sphincterotomized cases. Their use is limited to patients with over-aggregated cholangitis. Biliary AP should be treated on an urgent basis, preferably within the first 24 h, when choledocholithiasis has been documented by images or findings that are highly suggestive of persistent calculi in the bile duct, such as jaundice, progressive increase in liver function tests, or persistent dilation of the bile duct. There is no benefit of this treatment in the absence of these manifestations, in case of mild biliary AP or as a diagnostic test prior to cholecystectomy. Endoscopic ultrasonography (EUS) has been used as a platform for the minimally invasive treatment of pseudocyst with necrosis in the pancreatic wall [94-96].

8. Complications

8.1 Organ Failure

It is defined for three systems, respiratory– PaO_2/FiO_2 = 300, cardiovascular– use of inotropic agents, and renal– creatinine = 171 mmol/L or 2.0 mg/dL, in a 24-h period, as a score of ≥2 in Marshall's modified system which is preferred over the SOFA system because it is more simplified, universal, and stratifies severity especially in case of critically ill patients on inotropic and ventilatory support; both these systems may be used at the time of admission as well as on a daily basis. Organ failure may be transient in nature if it resolves in <48 h, and persistent if it persists for ≥48 h with mortality up to 30% [44, 66].

8.2 Systemic Complications

a) Exacerbation of pre-existing co-morbidities including the coronary disease, chronic liver disease, Chronic Obstructive Pulmonary Disease, acute renal failure, and intravascular disseminated coagulation.

b) Abdominal compartment syndrome is defined as a concomitant organ failure with intra-abdominal pressure > 20 mmHg developing as a consequence of aggressive fluid resuscitation, manifested in the form of abdominal distension, oliguria, or increased assisted mechanical ventilation. The syndrome is managed by 1) decreasing the contribution of liquids, 2) measuring the intra-vesical pressure using a urinary catheter, c) reducing the ventilatory tidal volume, and d) using nasogastric and rectal tubes. If these measures do not turn out to be effective, surgical decompression is preferred [71, 97].

c) Post-AP endocrine dysfunction (prediabetes and DM2) develops in 20%–30% of the cases, while the exocrine dysfunction (CP) develops in one-third or 50% of the cases. Association with pancreatic exocrine dysfunction has not been observed for 60% of the patients with DM2 because it recovers over time in these patients [98].

d) Other complications such as thrombosis of the portal vein, ascites by thrombosis of the superior mesenteric vein, and/or splenic aneurysm may occur after several weeks of hospitalization. Gastric dysfunction, necrosis of the colon, acidosis, respiratory distress syndrome, gastric varices, retroperitoneal hemorrhage, and gastrointestinal ileus, pleural effusion, aneurysms in the splenic, renal, or gastroduodenal arteries, and gastric hematoma have also been reported in the literature [69].

8.3 Local Complications

Local complications are suspected when persistent abdominal pain or recurrent increase in the levels of pancreatic enzymes are observed along with organ failure and/or signs of SIRS. These complications, by themselves, do not define the severity of AP. They are described by CT on the basis of their location (pancreatic, peri-pancreatic, or other), content (liquid, solid, or gas), and thickness of the wall (thin or thick) [99]. Currently, abdominal CT serves as a non-invasive diagnostic tool for the detection of collections [54, 100]. There are four types of collections, which appear in the following order:

1. Acute liquid collection, which appears before four weeks, and is associated with interstitial edematous AP in the absence of necrosis [74]. It is homogeneous, with dense liquid, not encapsulated, and confined to the peri-pancreatic fascia. Most of these are sterile and have a spontaneous resolution, which makes their management conservative.

2. Acute necrotic collection or PAN, which appears in the first four weeks. It may be sterile or infected. In the initial phases, the collection is a mixture of solid and semi-solid tissue, which subsequently becomes more liquid in nature and encapsulated (PAN encapsulated sterile). Infected PAN rarely appears in the first two weeks, and is suspected after this time period prior to the onset of fever, leukocytosis, and pain. Abdominal growth is generally monomicrobial and occurs more frequently by gram-negative bacilli. CT, in this case, demonstrates gas in the presence of necrosis. If sterile, it is managed conservatively and requires therapy only in rare cases exhibiting obstruction of a nearby viscus, such as that in the stomach, duodenum, or bile duct [83, 101].

In current practice, any invasive intervention is avoided for at least four weeks, when the encapsulation has demarcated the boundary between the necrotic tissue and the healthy tissue, forming a mature wall around it, which allows the drainage and debridement easier, reducing the risk of complications and death. If the patient exhibits progressive sepsis or is in unstable conditions, percutaneous drainage of the collection is sufficient to reduce the sepsis, allowing the delay of four weeks to be continued. It is possible to treat almost 60% of the patients with PAN non-invasively with a low risk of death [83].

In patients who develop severe AP and infected PAN or persistent liquid collections, the treatment comprises administration of antibiotics, CT-guided percutaneous drainage if necessary, and after a delay of several weeks, minimally invasive debridement (necrosectomy) may be performed using percutaneous, endoscopic, laparoscopic, or assisted retroperitoneal approaches.

This minimally invasive approach is superior to the traditional open necrosectomy in terms of the risk of major complications or death, and approximately one-third of the patients treated using this method do not require debridement. The drained liquid is Gram stained and cultured. Only a small percentage of patients with infected PAN may be treated only with the use of antibiotics [83, 101].

3. Pseudocyst, which appears around four weeks after, is an oval or round collection encapsulated by a fibrous wall, and a well-defined granulation in the extrapancreatic tissue without necrosis or with minimal necrosis with a homogeneous composition. These collections are usually asymptomatic; when symptoms appear, they are non-specific. If the pseudocyst is asymptomatic, it is managed conservatively, since it resolves spontaneously in >50% of the cases. If the pseudocyst is symptomatic, it becomes infected or exhibits increased size on consecutive images, and should be intervened mainly with endoscopic techniques [99, 102, 103].

4. Abscess, which appears after four weeks in the context of PAN, is a heterogeneous and encapsulated collection. More than 80% of the deaths associated with AP are attributed to the septic complications of PAN with a bacterial infection. It is suspected by the clinical evolution of the patient, or by the presence of gas. Its management is similar to that in the case of infected PAN [104]. Other local complications include pancreatic fistula, pseudocyst or pancreatocutaneous fistula, pseudo-aneurysm of the pancreatic artery, portal vein thrombosis, and superior mesenteric (manifested by ascites of recent onset) and/or splenic aneurysm which may occur several weeks after hospitalization, and should be detected and treated in an adequate and timely manner [69, 99]. Hemorrhage of pancreatic bed or retroperitoneum should be managed according to the etiology. In the case of aneurysm rupture, embolization is indicated, which if not resolved, surgery should be performed. Intramural hematomas in the absence of bleeding or other complications are managed conservatively. Otherwise, embolization may be opted as a safe and minimally invasive approach, reserving surgery for selected cases only [105, 106].

9. Surgical Treatment

In patients with mild biliary AP, cholecystectomy should be performed at an early stage (first 48 h after admission), resulting in the shortening of hospital stay compared to when it is performed after the resolution of pain and normalization of the enzymes. A delay increases the risk of recurrent biliary AP, and not the risk of complications [107, 108]. Biliary PAN surgery is delayed until inflammation occurs and the liquid collections stabilize, decrease, or disappear, which happens around six weeks after [108, 109].

10. Recurrent AP

It is characterized by episodes of AP occurring in more than one occasion by the normal morpho-functional adjustment of the gland. However, CP may be observed in the first episode of AP as well as in the following episodes. It is idiopathic in 30% of the cases, although in majority of cases, the cause is identified, which is mainly one of the following: choledocholithiasis or sludge and bile crystals in the common bile duct, dysfunction of the sphincter of Oddi, anatomical ductal variants that interfere with the exit of the pancreatic juice, obstruction in the main pancreatic duct or at the pancreaticobiliary junction, genetic mutations, and prolonged consumption of alcohol. In 80% of the cases, it is managed with cholecystectomy, and eventually, ERCP with sphincterotomy.

Ursodeoxycholic acid has also been reported to be effective in the treatment of biliary sludge [1, 110, 111]. A recent study demonstrated that longstanding pre-existing chronic pancreatitis serves as a strong risk factor for pancreatic cancer [112].

11. Prevention of Relapse

The rate of relapse of AP is 20% at 30 days. It is important to emphasize that recurrent abdominal pain is an essential factor for AP relapse. The risk factors for relapse observable in the first episode include severity, degree of necrosis and cause, and the use of antibiotics. The factors that reduce the risk of relapse include tolerance of solid diet and the absence of gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. The most common modifiable factors for risk of relapse include alcohol consumption and tobacco abuse. It has been observed that the patients who continue consuming alcohol exhibit a higher risk for AP relapse. Control of hyperlipidemia may also prevent relapse. Finally, in the case of biliary AP, a cholecystectomy should be performed before hospital discharge, which reduces the complication rate by 75%. If the procedure is delayed, it should be performed in a short ambulatory period, and the delay should not exceed a few weeks, as in such a case, the chances of recurrence increase by >30%. In patients with severe PAN or AP, cholecystectomy is postponed until the inflammation decreases, as it improves visibility at the time of surgery. In patients who are not candidates for surgery, biliary endoscopy may assist in reducing, although not eliminating, the risk of recurrence of acute cholecystitis or biliary colic [34, 113].

12. Conclusions

The main etiological causes of AP are alcohol consumption, gallstones, hypertriglyceridemia, and biliary stones. The clinical signs and symptoms, as well as the diagnostic criteria for AP, have been well established by multiple studies available in the literature. Multiple scoring systems have been applied to predict the severity, prognosis, and mortality associated with AP. It may be concluded that Ranson's criteria do have its advantages when approaching the patient in the Emergency Room or at the time of admission, although the APACHE II score definitely forms the basis for constant clinical-laboratory combined monitoring. Early and vigorous administration of IV fluids, mainly ringers' lactate, is important during the first 12–24 h of management of AP. In patients with mild biliary AP, cholecystectomy should be performed at an early stage (in the first 48 h after admission), which results in the shortening of hospital stay. Larger trials are required to investigate the role of heparanase inhibitors in the management of AP.

Author Contributions

All the authors have made substantive contributions to the article and assume full responsibility for its content.

Competing Interests

The authors declare no conflict of interest.

References

1. Testoni PA. Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment. World J Gastroenterol. 2014; 20: 16891-16901.
2. Portelli M, Jones CD. Severe acute pancreatitis: Pathogenesis, diagnosis and surgical management Hepatobiliary Pancreat Dis Int. 2017; 16: 155-159.
3. Gullo L, Migliori M, Oláh A, Farkas G, Levy P, Arvanitakis C, et al. Acute pancreatitis in five European countries: Etiology and mortality. Pancreas. 2002; 24: 223-227.
4. Xiao AY, Tan MLY, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: A systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016; 1: 45-55.
5. Sultan S, Falck–Ytter Y, Inadomi JM. The AGA institute process for developing clinical practice guidelines part one: Grading the evidence. Clin Gastroenterol Hepatol. 2013; 11: 329-332.
6. Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedrich JO, Nathens A, et al. Clinical practice guideline: Management of acute pancreatitis. Can J Surg. 2016; 59: 128-140.
7. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013; 13: e1-e15.
8. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: A systematic review. Pancreas. 2006; 33: 323-330.
9. Tryliskyy Y, Bryce GJ. Post-ERCP pancreatitis: Pathophysiology, early identification and risk stratification. Adv Clin Exp Med. 2018; 27: 149-154.
10. Forsmark CE, Swaroop Vege S, Wilcox CM. Acute pancreatitis. N Engl J Med. 2016; 375: 1972-1981.
11. Habtezion A. Inflammation in acute and chronic pancreatitis. Curr Opin Gastroenterol. 2015; 31: 395-399.
12. Rawla P, Sunkara T, Thandra KC, Gaduputi V. Hypertriglyceridemia-induced pancreatitis: Updated review of current treatment and preventive strategies. Clin J Gastroenterol. 2018; 11: 441-448.
13. Mandalia A, Wamsteker EJ, DiMagno MJ. Recent advances in understanding and managing acute pancreatitis. Version 2. F1000Res. 2018; 7. pii: F1000
14. Pang Y, Kartsonaki C, Turnbull I, Guo Y, Yang L, Bian Z, et al. Metabolic and lifestyle risk factors for acute pancreatitis in Chinese adults: A prospective cohort study of 0.5 million people. PLoS Med. 2018; 15: e1002618.
15. Greer JB, Thrower E, Yadav D. Epidemiologic and mechanistic associations between smoking and pancreatitis. Curr Treat Options Gastroenterol. 2015; 13: 332-346.
16. Alsamarrai A, Das SLM, Windsor JA, Petrov MS. Factors that affect risk for pancreatic disease in the general population: A systematic review and meta-analysis of prospective cohort studies. Clin Gastroenterol Hepatol. 2014; 12: 1635-1644.
17. Ye X, Lu G, Huai J, Ding J. Impact of smoking on the risk of pancreatitis: A systematic review and meta-analysis. PLoS One. 2015; 10: e0124075.
18. Tenner S. Drug induced acute pancreatitis: Does it exist? World J Gastroenterol. 2014; 20: 16529-16534.
19. Rawla P, Raj JP. Doxycycline-induced acute pancreatitis: A rare adverse event. Gastroenterology Res. 2017; 10: 244-246.

20. Hasan A, Moscoso DI, Kastrinos F. The role of genetics in pancreatitis. Gastrointest Endosc Clin N Am. 2018; 28: 587-603.
21. Martinez-Barona S, Ribes-Koninckx C. Genetics in idiopathic pancreatitis and acute recurrent pancreatitis. Rev Esp Enferm Dig. 2017; 109: 478-479.
22. Sahin-Toth M. Genetic risk in chronic pancreatitis: The misfolding-dependent pathway. Curr Opin Gastroenterol. 2017; 33: 390-395.
23. Majumder S, Takahashi N, Chari ST. Autoimmune pancreatitis. Dig Dis Sci. 2017; 62: 1762-1769.
24. Berger Z, Mancilla C. Is autoimmune pancreatitis a subclass of chronic pancreatitis? Pancreatology. 2017; 17: 55.
25. Wayne M, Delman KA, Kurt T, Grossi R, Sabatini M, Cooperman A. Autoimmune pancreatitis: Unveiling a hidden entity. Arch Surg. 2005; 140: 1104-1107.
26. Sureka B, Rastogi A. Autoimmune pancreatitis. Pol J Radiol. 2017; 82: 233-239.
27. Hart PA, Krishna SG, Okazaki K. Diagnosis and management of autoimmune pancreatitis. Curr Treat Options Gastroenterol. 2017; 15: 538-547.
28. Hasanovic J, Agic M, Rifatbegovic Z, Mehmedovic Z, Jakubovic-Cickusic A. Pancreatic injury in blunt abdominal trauma. Med Arch. 2015; 69: 130-132.
29. Rawla P, Bandaru SS, Vellipuram AR. Review of Infectious etiology of acute pancreatitis. Gastroenterology Res. 2017; 10: 153-158.
30. Mikolasevic I, Milic S, Orlic L, Poropat G, Jakopcic I, Franjic N, et al. Metabolic syndrome and acute pancreatitis. Eur J Intern Med. 2016; 32: 79-83.
31. Yoon SB, Choi MH, Lee IS, Lim C-H, Kim JS, Cho YK, et al. Impact of body fat and muscle distribution on severity of acute pancreatitis. Pancreatology. 2017; 17: 188-193.
32. Binker MG. Acute pancreatitis: The stress factor. World J Gastroenterol. 2014; 20: 5801-5807.
33. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017; 17: 155-165.
34. Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: Similarities and differences. Dig Dis Sci. 2017; 62: 1683-1691.
35. Dick JF, Gardner TB, Merrens EJ. Acute pancreatitis: New developments and strategies for the hospitalist. J Hosp Med. 2016; 11: 724-729.
36. Phillip V, Steiner JM, Algül H. Early phase of acute pancreatitis: Assessment and management. World J Gastrointest Pathophysiol. 2014; 5: 158-168.
37. Valette X, du Cheyron D. Cullen's and Grey Turner's signs in acute pancreatitis. N Engl J Med. 2015; 373: e28.
38. Basnayake C, Ratnam D. Blood tests for acute pancreatitis. Aust Prescr. 2015; 38: 128-1230.
39. Kaw M, Singh S. Serum lipase, C-reactive protein, and interleukin-6 levels in ERCP-induced pancreatitis. Gastrointest Endosc. 2001; 54: 435-440.
40. Ismail OZ, Bhayana V. Lipase or amylase for the diagnosis of acute pancreatitis? Clin Biochem. 2017; 50: 1275-1280.
41. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013; 108: 1400-1415; 1416.
42. Arvanitakis M, Delhaye M, De Maertelaere V, Bali M, Winant C, Coppens E, et al. Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis. Gastroenterology. 2004; 126: 715-723.

43. Štimac D, Miletić D, Radić M, Krznarić I, Mazur-Grbac M, Perković D, et al. The role of nonenhanced magnetic resonance imaging in the early assessment of acute pancreatitis. Am J Gastroenterol. 2007; 102: 997-1004.
44. Quinlan JD. Acute pancreatitis. Am Fam Physician. 2014; 90: 632-639.
45. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. Gut. 2012; 62: 102-111.
46. Sarr MG. 2012 revision of the Atlanta classification of acute pancreatitis. Pol Arch Med Wewn. 2013; 123: 118-124.
47. Zaheer A, Singh VK, Qureshi RO, Fishman EK. The revised Atlanta classification for acute pancreatitis: updates in imaging terminology and guidelines. Abdom Imaging. 2012; 38: 125-136.
48. Coffey MJ, Nightingale S, Ooi CY. Tu1494： Early prediction of severity in acute paediatric pancreatitis. Gastroenterology. 2012; 142: S-848.
49. Lippi G, Valentino M, Cervellin G. Laboratory diagnosis of acute pancreatitis: In search of the Holy Grail. Crit Rev Clin Lab Sci. 2012; 49: 18-31.
50. Winslet M, Hall C, London NJ, Neoptolemos JP. Relation of diagnostic serum amylase levels to aetiology and severity of acute pancreatitis. Gut. 1992; 33: 982-986.
51. Buxbaum J, Quezada M, Chong B, Gupta N, Yu CY, Lane C, et al. The Pancreatitis Activity Scoring System predicts clinical outcomes in acute pancreatitis: Findings from a prospective cohort study. Am J Gastroenterol. 2018; 113: 755-764.
52. Wilson J, Zarabi S. BET 1: SIRS criteria as a way of predicting mortality in acute pancreatitis. Emerg Med J. 2017; 34: 621-622.
53. Kiriyama S, Gabata T, Takada T, Hirata K, Yoshida M, Mayumi T, et al. New diagnostic criteria of acute pancreatitis. J Hepatobiliary Pancreat Sci. 2009; 17: 24-36.
54. Aphinives P, Karunasumetta C, Bhudhisawasdi V, Saesaew OT. Acute pancreatitis: Assessment severity with Ranson score and CT evaluation. J Med Assoc Thai. 2011; 94: 437-440.
55. Rawla P, Thandra KC, Sunkara T. Pancreatic cancer and obesity: Epidemiology, mechanism, and preventive strategies. Clin J Gastroenterol. 2019; doi: 10.1007/s12328-019-00953-3.
56. Harshit Kumar A, Singh Griwan M. A comparison of APACHE II, BISAP, Ranson's score and modified CTSI in predicting the severity of acute pancreatitis based on the 2012 revised Atlanta Classification. Gastroenterol Rep. 2018; 6: 127-131.
57. Yang L, Liu J, Xing Y, Du L, Chen J, Liu X, et al. Comparison of BISAP, Ranson, MCTSI, and APACHE II in predicting severity and prognoses of hyperlipidemic acute pancreatitis in chinese patients. Gastroenterol Res Pract. 2016; 2016: 1834256.
58. Chatzicostas C, Roussomoustakaki M, Vlachonikolis IG, Notas G, Mouzas I, Samonakis D, et al. Comparison of Ranson, APACHE II and APACHE III scoring systems in acute pancreatitis. Pancreas. 2002; 25: 331-335.
59. Khanna AK, Meher S, Prakash S, Tiwary SK, Singh U, Srivastava A, et al. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. HPB Surg. 2013; 2013: 367581.

60. Tan YHA, Rafi S, Tyebally Fang M, Hwang S, Lim EW, Ngu J, et al. Validation of the modified Ranson versus Glasgow score for pancreatitis in a Singaporean population. ANZ J Surg. 2017; 87: 700-703.
61. Gray R, Cagliani J, Amodu LI, Nauka P, Villacres B, Santos T, et al. Maximizing the use of scoring systems in the prediction of outcomes in acute pancreatitis. Digestion. 2019; 99: 166-171.
62. Aggarwal A, Manrai M, Kochhar R. Fluid resuscitation in acute pancreatitis. World J Gastroenterol. 2014; 20: 18092.
63. Harrison DA, D'Amico G, Singer M. The Pancreatitis Outcome Prediction (POP) Score: A new prognostic index for patients with severe acute pancreatitis. Crit Care Med. 2007; 35: 1703-1708.
64. Dellinger EP, Forsmark CE, Layer P, Lévy P, Maraví-Poma E, Petrov MS, et al. Determinant-based classification of acute pancreatitis severity. Ann Surg. 2012; 256: 875-880.
65. Bollen TL, Singh VK, Maurer R, Repas K, van Es HW, Banks PA, et al. Comparative evaluation of the modified CT severity index and CT severity index in assessing severity of acute pancreatitis. AJR Am J Roentgenol. 2011; 197: 386-392.
66. Chen C, Huang Z, Li H, Song B, Yuan F. Evaluation of extrapancreatic inflammation on abdominal computed tomography as an early predictor of organ failure in acute pancreatitis as defined by the revised Atlanta classification. Medicine. 2017; 96: e6517.
67. Li Y, Zhao Y, Feng L, Guo R. Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study. BMJ Open. 2017; 7: e013206.
68. Vege SS, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial medical treatment of acute pancreatitis: American gastroenterological association institute technical review. Gastroenterology. 2018; 154: 1103-1139.
69. Zerem E. Treatment of severe acute pancreatitis and its complications. World J Gastroenterol. 2014; 20: 13879.
70. Leppaniemi A, Johansson K, De Waele JJ. Abdominal compartment syndrome and acute pancreatitis. Acta Clin Belg. 2007; 62: 131-135.
71. Jaipuria J, Bhandari V, Chawla AS, Singh M. Intra-abdominal pressure: Time ripe to revise management guidelines of acute pancreatitis? World J Gastrointest Pathophysiol. 2016; 7: 186-198.
72. Goulden MR. The pain of chronic pancreatitis: A persistent clinical challenge. Br J Pain. 2013; 7: 8-22.
73. Gachago C, Draganov PV. Pain management in chronic pancreatitis. World J Gastroenterol. 2008; 14: 3137-3148.
74. John B, Srinivasan G, Venkatakrishnan L, Sambandam S, Singh G, Kaur M, et al. Current concepts in the management of acute pancreatitis. J Family Med Prim Care. 2016; 5: 752-758.
75. Iqbal U, Anwar H, Scribani M. Ringer's lactate versus normal saline in acute pancreatitis: A systematic review and meta-analysis. J Dig Dis. 2018; 19: 335-341.
76. de-Madaria E, Herrera-Marante I, Gonzalez-Camacho V, Bonjoch L, Quesada-Vazquez N, Almenta-Saavedra I, et al. Fluid resuscitation with lactated Ringer's solution vs normal saline in acute pancreatitis: A triple-blind, randomized, controlled trial. United European Gastroenterol J. 2018; 6: 63-72.

77. Horibe M, Nishizawa T, Suzuki H, Minami K, Yahagi N, Iwasaki E, et al. Timing of oral refeeding in acute pancreatitis: A systematic review and meta-analysis. United European Gastroenterol J. 2016; 4: 725-732.
78. Hegazi RA, DeWitt T. Enteral nutrition and immune modulation of acute pancreatitis. World Journal of Gastroenterology. 2014; 20: 16101.
79. Oláh A, Jr LR. Enteral nutrition in acute pancreatitis: A review of the current evidence. World J Gastroenterol. 2014; 20: 16123.
80. Ignatavicius P, Vitkauskiene A, Pundzius J, Dambrauskas Z, Barauskas G. Effects of prophylactic antibiotics in acute pancreatitis. HPB. 2012; 14: 396-402.
81. Jiang K, Huang W, Yang XN, Xia Q. Present and future of prophylactic antibiotics for severe acute pancreatitis. World J Gastroenterol. 2012; 18: 279-284.
82. Mourad MM, Evans R, Kalidindi V, Navaratnam R, Dvorkin L, Bramhall SR. Prophylactic antibiotics in acute pancreatitis: Endless debate. Ann R Coll Surg Engl. 2017; 99: 107-112.
83. Boumitri C, Brown E, Kahaleh M. Necrotizing pancreatitis: Current management and therapies. Clinical endoscopy. 2017; 50: 357-365.
84. Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: A randomized, double-blind, placebo-controlled study. Ann Surg. 2007; 245: 674-683.
85. Zhang MM, Cheng JQ, Lu YR, Yi ZH, Yang P, Wu XT. Use of pre-, pro- and synbiotics in patients with acute pancreatitis: A meta-analysis. World J Gastroenterol. 2010; 16: 3970-3978.
86. Gou S, Yang Z, Liu T, Wu H, Wang C. Use of probiotics in the treatment of severe acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials. Crit Care. 2014; 18: R57.
87. Yue Q, Gao G, Zou G, Yu H, Zheng X. Natural products as adjunctive treatment for pancreatic cancer: recent trends and advancements. Biomed Res Int. 2017; 2017: 8412508.
88. Stigliano S, Archibugi L, Zerboni G, Delle Fave G, Capurso G. The use of complementary and alternative medicine is frequent in patients with pancreatic disorders. J Clin Gastroenterol. 2016; 50: S161-S163.
89. Ceranowicz P, Dembinski A, Warzecha Z, Dembinski M, Cieszkowski J, Rembisz K, et al. Protective and therapeutic effect of heparin in acute pancreatitis. J Physiol Pharmacol. 2008; 59: 103-125.
90. Pupelis G, Plaudis H, Grigane A, Zeiza K, Purmalis G. Continuous veno-venous haemofiltration in the treatment of severe acute pancreatitis: 6-year experience. HPB. 2007; 9: 295-301.
91. Pupelis G, Plaudis H, Zeiza K, Drozdova N, Mukans M, Kazaka I. Early continuous veno-venous haemofiltration in the management of severe acute pancreatitis complicated with intra-abdominal hypertension: Retrospective review of 10 years' experience. Ann Intensive Care 2012; 20: S21.
92. Xu J, Tian X, Zhang C, Wang M, Li Y. Management of abdominal compartment syndrome in severe acute pancreatitis patients with early continuous veno-venous hemofiltration. Hepato-gastroenterology. 2013; 60: 1749-1752.
93. Khamaysi I, Singh P, Nasser S, Awad H, Chowers Y, Sabo E, et al. The role of heparanase in the pathogenesis of acute pancreatitis: A potential therapeutic target. Sci Rep. 2017; 7: 715.
94. Fiocca F, Santagati A, Ceci V, Donatelli G, Pasqualini MJ, Moretti MG, et al. ERCP and acute pancreatitis. Eur Rev Med Pharmacol Sci. 2002; 6: 13-17.

95. Canlas KR, Branch MS. Role of endoscopic retrograde cholangiopancreatography in acute pancreatitis. World J Gastroenterol. 2007; 13: 6314-6320.
96. Lee HS, Chung MJ, Park JY, Bang S, Park SW, Song SY, et al. Urgent endoscopic retrograde cholangiopancreatography is not superior to early ERCP in acute biliary pancreatitis with biliary obstruction without cholangitis. PLoS One. 2018; 13: e0190835.
97. De Waele JJ, Leppäniemi AK. Intra-abdominal hypertension in acute pancreatitis. World J Surg. 2009; 33: 1128-1133.
98. Das SL, Kennedy JI, Murphy R, Phillips AR, Windsor JA, Petrov MS. Relationship between the exocrine and endocrine pancreas after acute pancreatitis. World J Gastroenterol. 2014; 20: 17196-17205.
99. Upchurch E. Local complications of acute pancreatitis. Br J Hosp Med. 2014; 75: 698-702.
100. Balthazar EJ. Acute Pancreatitis: Assessment of severity with clinical and CT evaluation. Radiology. 2002; 223: 603-613.
101. Buchler MW, Gloor B, Muller CA, Friess H, Seiler CA, Uhl W. Acute necrotizing pancreatitis: Treatment strategy according to the status of infection. Ann Surg. 2000; 232: 619-626.
102. Kim KO, Kim TN. Acute pancreatic pseudocyst: Incidence, risk factors, and clinical outcomes. Pancreas. 2012; 41: 577-581.
103. Byrne MF, Mitchell RM, Baillie J. Pancreatic pseudocysts. Curr Treat Options Gastroenterol. 2002; 5: 331-338.
104. Srikanth G, Sikora SS, Baijal SS, Ayyagiri A, Kumar A, Saxena R, et al. Pancreatic abscess: 10 years experience. ANZ J Surg. 2002; 72: 881-886.
105. Evans RP, Mourad MM, Pall G, Fisher SG, Bramhall SR. Pancreatitis: Preventing catastrophic haemorrhage. World J Gastroenterol. 2017; 23: 5460-5468.
106. Flati G, Andren-Sandberg A, La Pinta M, Porowska B, Carboni M. Potentially fatal bleeding in acute pancreatitis: Pathophysiology, prevention, and treatment. Pancreas. 2003; 26: 8-14.
107. Navadgi S, Pandanaboyana S, Windsor JA. Surgery for acute pancreatitis. Indian J Surg. 2015; 77: 446-452.
108. Werner J, Feuerbach S, Uhl W, Buchler MW. Management of acute pancreatitis: From surgery to interventional intensive care. Gut. 2005; 54: 426-436.
109. Busquets J, Fabregat J, Pelaez N, Millan M, Secanella L, Garcia-Borobia F, et al. Factors influencing mortality in patients undergoing surgery for acute pancreatitis. Pancreas. 2013; 42: 285-292.
110. Nordback I, Pelli H, Lappalainen–Lehto R, Järvinen S, Räty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: A randomized controlled trial. Gastroenterology. 2009; 136: 848-855.
111. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol. 2016; 14: 738-746.
112. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: Global trends, etiology and risk factors. World J Oncol. 2019; 10: 10-27.
113. Guda NM, Romagnuolo J, Freeman ML. Recurrent and relapsing pancreatitis. Curr Gastroenterol Rep. 2011; 13: 140-149.

Enjoy *OBM Hepatology and Gastroenterology* by:

1. Submitting a manuscript
2. Joining in volunteer reviewer bank
3. Joining Editorial Board
4. Guest editing a special issue

For more details, please visit:
http://www.lidsen.com/journals/hg