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Review Article

Management of Severe Acute Pancreatitis

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Abstract

Acute pancreatitis is one of the most common causes of hospitalisation from gastrointestinal diseases. The causes of pancreatitis vary between countries. Acute pancreatitis is classified based on Revised Atlanta classification 2013 as mild, moderately severe and severe acute pancreatitis. Acute pancreatic severity can be stratified by scoring systems such as Ranson's score, BISAP score, APACHE-II score, SOFA score. In severe acute pancreatitis, to diagnose, abdominal pain raised amylase or lipase, supported imaging finding and organ failure. Organ failure can be diagnosed by using Modified Marshall Scoring System. Management is started conservatively, which are fluid resuscitation, enteral nutrition, analgesics, and antibiotics. Surgical management is indicated when infected pancreas necrosis is detected. In this review, we will discuss the current management based on recent research.

Introduction

Acute pancreatitis is one of the most common causes of hospitalisation from gastrointestinal diseases, with a global incidence ranging from 5-30 cases per 100,000 population per year. In America, pancreatitis causes more than 800,000 hospital visits and costs more than 2.6 billion dollars [1].

The causes of pancreatitis vary between countries. Alcohol is still the dominant disease in Western countries, while in Eastern countries, especially Asia, the most common cause is biliary disease (49-54%) [1], [2]. Others were caused by drug reactions, pancreatic and cystic malignancies, and hypertriglyceridemia [2].

Grading and Severity

Revised Atlanta classification 2013 are commonly used to categorise acute pancreatitis, which is mild, moderately severe and severe acute pancreatitis. Most of the acute pancreatitis were mild, in which organ failure or complications were not found. In moderately severe acute pancreatitis, Organ failure was transiently found in less than 48 hours [3], [4], [5]. Meanwhile, in severe acute pancreatitis (SAP), organ failure was seen for more than 48 hours. Moderately severe and severe acute pancreatitis manifest in systemic and local complication. The systemic complication in moderately severe acute pancreatitis was seen in chronic renal failure patient who presents with acute symptoms. Local complications usually manifest in the pancreatic and peri-pancreatic fluid collection. Those collections generally appear in the late phase of pancreatitis [4].

Acute pancreatic severity is influenced by organ failure. Revised Atlanta recommend Modified Marshall scoring system as the main tool in determining organ failure [4]. Modified Marshall scoring system (Table 1) include respiratory, cardiovascular and renal systems score. Score more than 2 of any organs indicate organ failure. Acute pancreatic severity can be stratified by scoring systems such as Ranson's score, BISAP score, APACHE-II score, SOFA score. Ranson's criteria are used within 48 hours of the onset of the attack. APACHE-II score of 9 or more is considered as

severe pancreatitis. APACHE score can be observed during the course of acute pancreatitis. The disease is assumed as severe acute pancreatitis when the score is 3 or more. BISAP score is observed during the first 24 hours of admission to predict mortality before the onset of organ failure. BISAP score of more than 3 is related to 5-20% mortality [5].

Table 1: Modified Marshall scoring system [4]

ORGAN SYSTEM	0	1	2	3	4
Respiratory PO/FiO_2 (mmHg)	> 300	226-300	151-225	76-150	≤ 75
Renal Serum creatinine (µmol/liter)	≤ 100	101-200	201-350	351-500	> 500
Hepatic Serum bilirubin (µmol/liter)	≤ 20	21-60	61-120	121-240	> 240
Cardiovascular PAR	≤ 10,0	10,1-15,0	15,1-20	20,1-30	> 30,0
Hematologic Platelet / nl	> 120	81-120	51-80	21-50	≤ 20
Neurologic Glassgow coma score	15	13-14	10-12	7-9	≤ 6

Diagnosis

Revised Atlanta classification requires the presence of abdominal pain, the increment of amylase or lipase more than 3 times upper limit of the normal range, and supported radiographic findings. The abdominal pain characterised by epigastric pain, followed by nausea and vomiting. In physical examination, rebound tenderness, abdominal distention, Cullen's sign, Grey Turner's sign can be found. In severe condition, reduced bowel sound, hypotension can also be found. Pancreatic acinar cell leakage in interstitial space and absorption into circulation cause Increment in amylase and lipase [3], [4], [5]. Contrast-enhanced CT scan (CE-CT scan) is the standard radiographic imaging in detecting acute pancreatitis [3], [4], [5]. In severe acute pancreatitis, CE-CT scan can be used to find pancreatic gland necrosis and the local complications. Pancreatic gland necrosis completely appears in 4 days after the onset of SAP. Before that time, CE-CT scan cannot precisely detect pancreatic necrosis. Other radiographic modalities that were commonly used in diagnosing acute pancreatitis were ultrasonography, MRI. Ultrasonography has a limited role in diagnosing acute pancreatitis, especially in ileus patient. Abundant air volume in the intestine in ileus patient cause difficulty in the visualization of the pancreas. MRI is considered as a good alternative in detecting pancreatic necrosis, pancreatic collection and peri-pancreatic collection. Magnetic resonance cholangiopancreatography (MRCP) can be used as an alternative to ERCP to evaluate pancreatic duct [4], [5].

Management

Fluid resuscitation

In severe acute pancreatitis, the patient could have excessive vomiting, reduced oral intake, third space extravasation, respiratory losses, and diaphoresis. Therefore, fluid resuscitation becomes the most important step in managing severe acute pancreatitis [6]. It is recommended to be done as early as possible. Crystalloid is the preferred choice in resuscitation. There are many types of research (Table 2) showed Ringer Lactate as the replacement fluid has many beneficial effects. The solution has to be given 250-500 ml per hour in the first 12-24 hours. NaCl 0.9% is not recommended since it triggered hyperchloremic metabolic acidosis when it was given in a large volume [6].

Table 2: The beneficial effect of Lactated Ringer's solution in various research

Author	Journal, Year	Method	Conclusion
De 'Madaria et al., [7]	United European Gastroenterology Journal, 2018	RCT	Lactated Ringer (LR) is associated with a reduction of CRP levels. LR has an anti-inflammatory effect in patients with acute pancreatitis
Iqbal et al. [8]	Journal of Digestive Diseases, 2018	Meta-analysis	LR has anti-inflammatory effects and is associated with decreased risk of persistent SIRS at 24h, which is a marker of severe disease in AP patients
Choosakul et al. [9]	Pancreatology, 2018	RCT	LR solution was superior to NS in SIRS reduction in acute pancreatitis only in the first 24h. But SIRS at 48h and mortality were not different between LR and NS.
Wu et al. [10]	Clinical Gastroenterology and Hepatology, 2011	RCT	Patients with acute pancreatitis who were resuscitated with LR solution had reduced systemic inflammation compared with those who received saline.

Abbreviations: RCT (Randomized control trial); CRP (C-reactive protein); SIRS (Systemic inflammatory response syndrome); LR (Lactated Ringer's); NS (Normal saline).

Few parameters can be used to predict the outcome after fluid resuscitation, which is hematocrit and BUN. Hemoconcentration, which can be seen from hematocrit, develop in the hypovolemic condition in SAP. Hematocrit < 44%-47% is a risk factor for developing necrosis in the pancreas [6] Wu et al., revealed that hemoconcentration was related to increment in mortality rate among hospital transferred patients. BUN was also recommended by Wu et al., as a predictor of pancreas necrosis. If fluid resuscitation had been done, BUN was not decreased, then the patient would have increased risk of pancreas necrosis [10].

To monitor the responsiveness of resuscitation, beside BUN and hematocrit, the physician was recommended to monitor urine output. Urine output > 0.5 ml/kg BW/hour was suggested as the target. Lactate was also mentioned as the monitoring parameter. However, there is no evidence to apply this to severe acute pancreatitis [6].

Enteral nutrition

Enteral nutrition was recommended for severe acute pancreatitis over parenteral nutrition due to many beneficial effects as shown by few meta-analysis and trial (Table 3). Enteral nutrition may maintain the function and structure of intestinal mucosa [5], [11]. Enteral nutrition was suggested to be given as early as 48 hours of admission [13], [11] Early enteral nutrition could reduce mortality, multiple

organ failure and infection in comparison with late enteral nutrition and parenteral nutrition [12]. Parenteral nutrition was previously recommended as early intervention since it reduces the stimulation of pancreas to secrete enzymes, but it can lead to intestinal atrophy and altered intestinal barrier. As consequences, microorganisms from the gut will translocate to the systemic circulation through damaged intestinal epithelial cells causing sepsis. Furthermore, toxic products and inflammatory mediators also translocate because of increased intestinal permeability in the early stage of severe acute pancreatitis [11].

Table 3: Comparison of Enteral Nutrition and Total Parenteral Nutrition

Author	Journal, Year	Method	Conclusion
Qi et al. [14]	Journal of Parenteral and Enteral Nutrition, 2018	Meta-analysis	Comparing early EN to TPN showed a significant reduction in multiple organ failure and pancreatic related infections
Vieira et al. [15]	Acta Cirugica Brasileira, 2010	RCT	More complications occurred in the parenteral group, although the difference was not statistically significant. Infectious complications were significantly more frequent in the parenteral group ($p = 0.006$)
Li et al. [16]	Journal of International Medical Research, 2018	Meta-analysis	The duration of hospitalisation was significantly shorter in the EN than TPN group. Compared with TPN, EN had a lower risk of pancreatic infection and organ failure.
Yi et al. [17]	Internal Medicine, 2012	Meta-analysis	TEN was significantly superior to TPN when considering mortality, infectious complications, organ failure
Quan et al. [18]	Clinical Gastroenterology and Hepatology, 2011	Meta-analysis	Compared with TPN, EN was associated with a significantly lower incidence of pancreatic infection complications, MOF, and mortality

Abbreviations: RCT (randomized control trial), EN(enteral nutrition), TPN(total parenteral nutrition, MOF(multiple organ failure), TEN(Total Enteral nutrition).

In a comparison of nasogastric and nasojejunal feeding, many trials and meta-analysis (Table 4) showed no significant difference in mortality, complications and length of stay [19]. Nasogastric feeding was cheaper, easy to apply and simpler. Meanwhile, Nasojejunal feeding has to be done by interventional radiologist or endoscopy operator causing a delay in feeding and increment of cost.

Table 4: Comparison of Nasogastric Feeding and Nasojejunal Feeding

Author	Journal, Year	Method	Conclusion
Zhu et al. [20]	Gastroenterology Research and Practice, 2016	RCT	There were no significant differences in the incidences of mortality, infectious complications, digestive complications, or length of hospital stay between NG and NJ nutrition groups. NG nutrition was as safe and effective as NJ nutrition in with SAP
Chang et al. [21]	Critical Care 2013	Meta-analysis	There were no significant differences in the incidences of mortality between NGT and NJT groups. NG feeding is safe and well-tolerated compared with NJ feeding
Singh et al. [22]	Pancreas 2012	RCT	Early enteral feeding through NG was not inferior to NJ in patients with SAP. Infection complications and length of hospital stay were comparable in both groups.
Kumar et al. [23]	Journal of Clinical Gastroenterology, 2006	RCT	Enteral nutrition at a slow infusion is well tolerated by both NJ and NG routes in patients with SAP. Neither NJ nor NG feeding leads to recurrence or worsening of pain in SAP
Eatock et al. [24]	American Journal of Gastroenterology, 2005	RCT	The simpler, cheaper, and more easily used NG feeding is as good as NJ feeding in patients with objectively graded severe AP

Abbreviations: RCT (randomized control trial); NGT (nasogastric tube); NJ (naso-jejunal); AP (acute pancreatitis).

Antibiotics

Many researchers conclude that antibiotics were recommended to be given in severe acute pancreatitis patients who developed sepsis, pancreatic or extrapancreatic infection, infected necrosis systemic inflammatory response [25]. Antibiotic as prophylaxis does not decrease mortality and secondary infection significantly [5], [13]. It is given as prophylaxis when infection marker, such as procalcitonin, IL-6, is detected [25]. The recommended antibiotics in treating severe acute pancreatitis that covers gram-positive (Clostridium) and gram-negative (E. coli, Klebsiella, Pseudomonas, Proteus) as well as anaerobes such as imipenem, meropenem, ciprofloxacin, clindamycin and metronidazole [13], [25]. All these antibiotics have adequate penetration and bactericidal effect in infected pancreatic necrosis. Prolong use of antibiotics have a risk of multi drugs resistance and development of fungal infection which is related to a long hospital stay and poor outcome [5], [25].

Analgesics

Pain is one of the most complained problems of acute pancreatitis patients. Therefore, pain management needs to be given in the first 24 hours to maintain the patient's quality of life. There are many choices of analgesics, such as fentanyl, meperidine, non-steroid anti-inflammatory drugs. Pain management was based on WHO analgesic ladder which consist of 4 steps (Step 1: NSAID, Step 2: low potent opioid ± NSAID ± adjuvant drugs, Step 3: High potent opioid ± NSAID ± adjuvant drugs, Step 4: interventional treatment ± high potent opioid ± NSAID ± adjuvant drugs) [27]. Opioids had been reported in the past study as a trigger of spasm of the sphincter of Oddi but in a recent Cochrane review on five RCTs with a total of 227 patients showed no difference between opioids and other analgesic options regarding the risk of complications or clinically serious adverse events [26]. A meta-analysis that was made by Stigliano et al. concluded there was no credible evidence to avoid the use of morphine in managing pain in acute pancreatitis [28].

Somatostatin and octreotide

Somatostatin and its long-acting analogue octreotide are the inhibitors of exocrine pancreatic secretion and further prevents the release and activation of enzymes. The benefit of these medications is controversial. W Uhl et al. revealed that octreotide had no benefit in the treatment of acute pancreatitis [29]. However, Paran et al., showed that in their study, complication rate was lower in treatment group than in control group (sepsis [24% vs 76%, $p < 0.0002$], ARDS [28% vs 56%, $p = 0.04$]). Therefore, Paran et al., suggested that octreotide might have benefit in the treatment of severe acute pancreatitis

[30].

Surgical management

Surgical interventions are indicated when infected necrosis and gallstone obstruction causing biliary pancreatitis is detected. Delayed surgical intervention was suggested because it was related to lower incidences of multi-organ failure, uncontrolled bleeding and sepsis. Therefore, the recommendation is to delay the surgical intervention until the infected necrosis process stops expanding and by the time, the necrotic tissue will liquify. After it liquefies, percutaneous or endoscopic drainage of the infected collection can be ordered. Because of open necrosectomy was associated with high morbidity and mortality, minimally invasive surgical techniques are preferred as the next step of the Step-up approach if drainage by endoscopy failed [4]. Step up approach which was started with minimal invasive drainage technique and endoscopic necrosectomy, was concluded by Rasch et al. had significant decrement of morbidity and mortality in necrotising pancreatitis compared to primarily surgical intervention [31].

Conclusion

Severe acute pancreatitis is treated conservatively by fluid resuscitation, early enteral feeding, analgesic, and antibiotic. Ringer lactate is the recommended fluid resuscitation. Enteral feeding as early as 48 hours after admission is the recommended protocol. When dealing with pain, non-opioid and opioid can be used in severe acute pancreatitis. Antibiotics are indicated when infection markers are detected. Somatostatin and it's analogue show no benefit in the treatment of severe acute pancreatitis.

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