Timeliness of Early Intervention in Acute Pancreatitis: A Postprint

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Abstract

Acute pancreatitis is an inflammatory condition involving the pancreas and peripancreatic tissues, with severe acute pancreatitis (SAP) causing organ failure and high mortality. Early intervention within the first 24 hours following admission is critical for improving outcomes in SAP. Evidence indicates that early prediction of disease severity, adequate fluid resuscitation, and early enteral nutrition contribute to improved clinical outcomes. Non-selective prophylactic antibiotic administration and early ERCP are ineffective in SAP patients. However, most existing studies are limited by small sample sizes and low levels of evidence, necessitating further high-quality research to elucidate early treatment options for SAP patients.

Full Text

Preamble

The Significance of Early Intervention in Acute Pancreatitis

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Abstract

Acute pancreatitis is an inflammatory disease involving the pancreas and peripancreatic tissues. Severe acute pancreatitis (SAP) can lead to organ failure and carries a high mortality rate. Early intervention within the first 24 hours after admission is crucial for improving outcomes in SAP. Evidence suggests that early prediction of disease severity, adequate fluid resuscitation, and early enteral nutrition can improve clinical outcomes. However, routine prophylactic antibiotics and early ERCP are ineffective for SAP patients. Most existing

studies suffer from small sample sizes and low evidence levels, highlighting the need for more high-quality research to clarify early treatment strategies for SAP patients.

Keywords: Acute pancreatitis; Severe acute pancreatitis; Fluid therapy; Early intervention; Treatment

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Acute pancreatitis (AP) is an inflammatory process triggered by premature activation of pancreatic enzymes from various pathogenic factors, resulting in damage to the pancreas and surrounding tissues. Patients with severe AP often develop systemic inflammatory response syndrome (SIRS), leading to organ failure beyond the pancreas and potentially death. In the United States, AP ranks as the third most common cause of hospitalization for digestive diseases, with over 275,000 admissions annually, more than 2,000 deaths, and direct economic losses reaching $2.6 billion [1]. While over 80% of AP patients have mild disease with 0% mortality, the mortality rate for severe AP can reach 20-30% [2].

According to the Revised Atlanta Classification (RAC), AP is diagnosed when two of the following three criteria are met: (1) typical acute abdominal pain (upper abdominal pain, often radiating to the back); (2) serum amylase and lipase levels three times or more the upper limit of normal; and (3) characteristic imaging findings of AP. Mild acute pancreatitis (MAP) is defined as the absence of organ failure or local complications, requiring only symptomatic treatment for recovery. Moderately severe acute pancreatitis (MSAP) involves local complications and/or organ failure that resolves within 48 hours, with mortality approaching 0%. Severe acute pancreatitis (SAP) is characterized by organ failure lasting more than 48 hours, with a dangerous clinical course and high mortality [3, 4].

Research demonstrates that early diagnosis and treatment of SAP are critical for patient prognosis, particularly within the first 24 hours after admission—the "golden hours" for intervention [5]. Pancreatic ischemia resulting from inadequate effective circulating volume is considered a "second hit" to the pancreas following the initial inflammatory response. In terms of therapeutic timeliness, SAP shares similarities with acute coronary syndrome: timely restoration of pancreatic and systemic perfusion and control of the inflammatory response in the early disease course can help alleviate the condition and prevent multiple organ dysfunction. This review focuses on early SAP management, emphasizing severity prediction, early fluid resuscitation, and early enteral nutrition, while noting that prophylactic antibiotics and endoscopic retrograde cholangiopancreatography (ERCP) should not be routinely applied to SAP patients.

1. Severity Prediction

Admission assessment of AP patients is essential for treatment selection, as accurate prediction of disease trajectory enables timely adjustment of therapeutic

strategies and rational allocation of medical resources. Multiple scoring systems are available for predicting AP severity. Ranson and APACHE II are classic AP scoring tools, while BISAP and PASS are more recently developed. Compared with the long-standing Ranson and APACHE II scores, BISAP and PASS are relatively simpler to use and supported by higher-level evidence [6].

2. Fluid Resuscitation

SAP patients frequently experience severe systemic inflammatory responses that cause vasodilation, reduced effective circulating volume, and inadequate organ perfusion. Volume depletion can lead to pancreatic ischemia and necrosis, acting as a "second hit"that drives SAP progression. Based on this understanding, fluid resuscitation is widely considered the cornerstone of early SAP management [7].

Goal-directed therapy (GDT) involves monitoring fluid rate and volume through clinical and laboratory parameters including heart rate, blood pressure, mean arterial pressure, urine output, hematocrit (HCT), blood urea nitrogen (BUN), creatinine (Cr), central venous pressure, stroke volume variation, and intrathoracic blood volume. However, two RCTs evaluating GDT in SAP patients yielded conflicting conclusions [8, 9]. Wu et al. [8] found no significant differences in mortality, organ failure, or pancreatic necrosis rates between GDT and conventional fluid resuscitation. Wang et al.' s study [9] lacked statistical power due to insufficient sample size. Additionally, neither study demonstrated significant differences in fluid volume between GDT and control groups. Consequently, high-level evidence supporting GDT benefits in SAP patients is currently lacking, and optimal therapeutic targets for fluid resuscitation remain undefined.

Regarding fluid resuscitation rate, two RCTs showed that overly aggressive fluid administration (10-15 ml/kg · h vs. 5-10 ml/kg · h; HCT <35 vs. HCT 35) increased mortality and sepsis rates [10, 11]. Clinical experience also indicates that excessive fluid resuscitation can impair cardiopulmonary function, increase intra-abdominal pressure, and compromise organ perfusion. Therefore, appropriate fluid rate is crucial, and overly aggressive approaches should be abandoned. Current APA guidelines recommend an initial rate of 5-10 ml/kg · h, targeting heart rate reduction to 90-120/min, mean arterial pressure elevation to 65-85 mmHg, urine output of 0.5-1.0 ml/kg · h, and HCT maintenance at 35-44%. ACG guidelines suggest initial infusion at 250-500 ml/h with reassessment every 6 hours, halving the rate after BUN decreases [7]. The optimal window for fluid resuscitation is generally considered to be within 12-24 hours of admission, with minimal benefit from aggressive fluid therapy beyond this period [7].

Concerning fluid type, lactated Ringer' s solution contains physiological chloride concentrations and bicarbonate precursors, theoretically offering advantages over normal saline in reducing metabolic acidosis [12]. Multiple RCTs have shown that although lactated Ringer' s solution offers no advantage over normal saline in reducing mortality, pancreatic necrosis, or organ failure risk,

it helps decrease SIRS incidence and CRP levels, suggesting potential positive prognostic effects [8, 12, 13]. Conversely, two Chinese RCTs reported benefits of combining lactated Ringer' s solution with hydroxyethyl starch (HES) over lactated Ringer' s alone [14, 15]. Notably, in Zhao et al.' s study [14], HES showed advantage only in improving intra-abdominal hypertension (IAH) without significant differences in other endpoints. Du et al.' s study [15] lacked statistical power due to small sample size. Multiple studies have demonstrated that HES offers no advantage over crystalloids and increases risks of renal injury, coagulation abnormalities, and even mortality [16, 17]. In summary, high-quality evidence for optimal fluid type selection is lacking, and colloid benefits remain unproven. Lactated Ringer' s solution may be cautiously preferred, though it should be avoided in hypercalcemia-induced acute pancreatitis (e.g., from hyperparathyroidism).

3. Early Enteral Nutrition

Traditional management emphasized fasting (nil per os, NPO) as a critical component of AP treatment. "Gut rest" was believed to prevent further pancreatic stimulation and enzyme activation, thereby reducing pancreatitis severity. However, recent meta-analyses demonstrate that early enteral nutrition (within 24 hours of admission) protects intestinal mucosal epithelium and prevents bacterial translocation, thus reducing infection risk [18, 19].

One meta-analysis of 11 RCTs found that early oral feeding did not increase AP mortality (OR 0.59, 95% CI 0.22-1.59). Rather, early enteral nutrition reduced pancreatic necrosis severity (OR 2.47, 95% CI 1.41-4.35) and showed downward trends in other important endpoints including organ failure rates. Therefore, researchers advocate early oral feeding for AP patients who can tolerate it [19].

The meta-analysis also found enteral nutrition significantly superior to total parenteral nutrition in preventing infected pancreatic necrosis and organ failure (multiple organ failure: OR 0.41, 95% CI 0.27-0.63; single organ failure: OR 0.25, 95% CI 0.10-0.62). Thus, enteral nutrition is recommended for patients unable to tolerate oral feeding. Regarding enteral nutrition route, three RCTs found no significant differences between nasogastric (NG) and nasoenteral (NE) tubes (mortality: OR 1.01, 95% CI 0.44-2.30), suggesting NG tubes may be safely used in some AP patients. This raises the possibility of gradually replacing nasojejunal tubes with NG tubes. However, since SAP patients often have varying degrees of gastroparesis and pyloric obstruction, the definitive efficacy of NG tubes requires further clinical validation [19].

4. Prophylactic Antibiotics

While antibiotic use is unquestionably indicated for SAP with confirmed infection, routine prophylactic antibiotics for all SAP patients remains controversial. A recent meta-analysis of 10 RCTs (n=701) showed that prophylactic antibiotics trended toward reduced mortality (OR=0.66, 95%CI 0.42-1.04) and

significantly decreased infected necrosis (OR=0.56, 95%CI 0.36-0.86). However, subgroup analysis limited to post-2002 studies eliminated these trends [19]. The authors attributed this discrepancy to publication bias and methodological quality differences, as some pre-2002 RCTs lacked blinding [20]. Prophylactic antibiotics provided no clear benefits regarding organ failure or hospital length of stay. Therefore, routine prophylactic antibiotics are not recommended for AP patients without definitive infection evidence.

5. Early ERCP

Early ERCP was once considered important for acute biliary pancreatitis, based on the rationale that relieving biliary obstruction would reduce inflammatory processes and pancreatic necrosis. However, according to the 2018 American Gastroenterological Association AP guidelines, emergency ERCP does not reduce mortality (OR 0.67, 95%CI 0.26-1.75) or improve other major outcomes in biliary SAP patients without cholangitis (n=935), including multiple organ failure (OR 0.32, 95%CI 0.03-3.19), respiratory failure (OR 0.86, 95%CI 0.34-2.19), renal failure (OR 1.02, 95%CI 0.40-2.59), circulatory failure (OR 0.99, 95%CI 0.25-3.95), infected peripancreatic necrosis (OR 0.75, 95%CI 0.21-2.64), and necrotizing pancreatitis (OR 1.13, 95%CI 0.66-1.95) [19]. Therefore, ERCP indications in biliary pancreatitis should be acute suppurative cholangitis or persistent biliary obstruction, not SAP severity itself. In most biliary pancreatitis patients, the cause is microlithiasis with typically transient biliary obstruction. During the initial disease course, transaminases, biliary enzymes, and bilirubin gradually normalize, obviating the need for emergency ERCP.

6. Conclusion

The first 24 hours after admission represent a critical therapeutic window for AP patients. Early appropriate treatment reduces SAP mortality and prevents or mitigates organ failure and pancreatic necrosis. Early fluid resuscitation is the cornerstone of SAP management. Current guidelines recommend determining fluid volume and rate based on clinical signs and biochemical indicators (BUN, Hct), with lactated Ringer' s solution as the preferred choice. The optimal resuscitation period is within 12-24 hours of admission. Routine prophylactic antibiotics are not recommended. Early oral feeding or enteral nutrition is superior to fasting and total parenteral nutrition, and should be initiated as early as tolerated. Early ERCP is not recommended unless persistent biliary obstruction or acute cholangitis is present [18].

Since SAP represents a small proportion of AP patients and requires intensive treatment within 24 hours of presentation, clinical research is challenging. Existing studies are mostly single-center or few-center investigations with small sample sizes, and many are retrospective, resulting in high bias risk and low evidence levels. Therefore, we recommend conducting large-scale, multi-center, rigorously designed clinical studies, particularly high-quality real-world studies,

to guide future SAP management.

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Note: Figure translations are in progress. See original paper for figures.