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The state of the art in acute pancreatitis research

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Abstract: This paper comprehensively analyzes the treatment methods for acute pancreatitis. By delving into the advantages and disadvantages of various current treatment strategies in terms of efficacy, safety, and feasibility, it aims to provide a useful reference for clinical treatment. Furthermore, the paper also focuses on the shortcomings and challenges of current treatments, seeking to explore emerging therapeutic methods to improve patient outcomes and quality of life. To achieve this goal, the effectiveness and limitations of existing treatments are summarized, with attention paid to emerging strategies such as exosome therapy and targeted treatments, highlighting their potential as shown in clinical trials and practice. The paper further elaborates on the potential benefits these new treatments may offer to patients with acute pancreatitis, and discusses the current technical challenges and future directions. Ultimately, this paper aims to provide a reference for research and clinical treatment of acute pancreatitis. It hopes to offer useful information to medical professionals, scholars, and patients, aiding in a better understanding of the condition and treatment methods of acute pancreatitis, contributing to the improvement of cure rates and the enhancement of patients' quality of life.

1. The definition and epidemiology of acute pancreatitis

Acute pancreatitis (AP) is a serious inflammatory disease that involves acute intense inflammatory response and sudden damage to the pancreas. It is a life-threatening disease, with typical clinical manifestations of upper abdominal or back pain, accompanied by nausea, vomiting and fever. Acute pancreatitis may cause various severe complications, such as pancreatic necrosis, infection, ascites, etc. In recent years, the incidence of acute pancreatitis has increased globally, with about 13 to 45 per 100,000 cases per year[1]. Among them, the incidence rate of males is higher than that of females[2]. Lifestyle factors are one of the main causes of acute pancreatitis. The two most common factors are gallstones and alcohol abuse[3], and other possible factors include hyperlipidemia, viral infection, trauma, etc.

2. The symptoms of acute pancreatitis

The main symptom of AP is severe upper abdominal pain[4], which sometimes radiates to the back, worsens within a few hours after meals, and lasts for several hours to days. Patients may also experience nausea and vomiting[5], leading to dehydration and electrolyte imbalance. Abdominal swelling and tension indicate inflammation in the abdominal cavity, and severe patients may develop abdominal compartment syndrome and multiple organ failure, which are life-threatening[6]. Patients may also have fever, which may be related to the release of inflammatory mediators[4], biliary infection[5] or systemic response[6]. The appearance of jaundice indicates abnormal bilirubin metabolism, which may be caused by bile flow obstruction, resulting in yellowing of the skin and eyes. Jaundice[7,8] occurs in about 10%-20% of patients, reflecting the impact of the disease on multiple organ systems.

3. The main methods of treating acute pancreatitis

Fluid replenishment: AP is a common and life-threatening inflammatory disease that requires early supportive treatment, in which fluid therapy is the core[9]. Fluid therapy can correct fluid balance, stabilize blood pressure, reduce complications and mortality. It is usually recommended to perform aggressive fluid resuscitation within the first 24 hours after treatment, which is a free fluid administration strategy to achieve the desired effect. However, aggressive fluid resuscitation may also lead to complications such as respiratory failure[7-8], and even increase the risk of sepsis or death in patients[11]. Fluid resuscitation via the rectal route (FRVC) may be used as a supplementary therapy for early fluid resuscitation[10] in severe acute pancreatitis (SAP), but it has no significant advantage in terms of overall long-term prognosis[12].

Pain management: AP patients often have severe pain in the pancreatic region, which is the main reason and symptom for AP patients to be hospitalized[13]. Pain management requires a variety of drugs, including: Non-steroidal anti-inflammatory drugs (NSAIDS): such as acetaminophen and ibuprofen. NSAIDS can relieve mild to moderate pain, but should be used with caution, as they may damage the gastric mucosa and kidneys. Opioid analgesics: such as morphine and hydrocodone. Opioids[14] can be used for severe pain, but should be closely monitored, as they may cause respiratory depression and dependence. Proton pump inhibitors (PPI): such as omeprazole and esomeprazole. PPI can reduce the secretion of acidic gastric juice, relieve gastroesophageal reflux and ulcer formation caused by AP. And opioids are more effective than systemic local anesthesia in reducing the need for emergency analgesia[15]. While controlling pain, the patient's respiratory function and sedation effect should be monitored to achieve the best treatment effect.

Antibiotic therapy: AP patients may develop infections, such as pancreatic necrosis or cholangitis. Common antibiotics are: Ampicillin/sulbactam: a broad-spectrum antibiotic that can be used for mild or asymptomatic AP patients. Third-generation cephalosporins: such as cefotaxime, ceftriaxone, etc., have broad-spectrum antibacterial effects. They can be used for moderate to severe AP patients, and can cover more types of bacterial infections. Meropenem/tigecycline: a potent antibiotic combination that can be used for severe AP and complications caused by infection. This may be more effective for cases involving multiple bacterial infections or antibiotic resistance. Fluoroquinolones: such as levofloxacin, ciprofloxacin, etc., may have better efficacy for some bacterial infections. However, the role of these antibiotics in first-line treatment is still controversial, and they are generally only used when other antibiotics are ineffective or resistant. The use of antibiotics should be based on the results of bacterial culture and procalcitonin (PCT) levels. When PCT levels are elevated, it may indicate infection, and antibiotic therapy should be considered. During the course of the disease, PCT levels should be continuously tracked to assess the response to treatment. When PCT levels drop to normal or acceptable range, signs and symptoms of infection

improve, and the patient's condition is stable, antibiotics should be discontinued. Since most AP cases are sterile, antibiotic therapy for AP is not recommended. Many studies have shown that prophylactic antibiotics cannot effectively reduce the risk of pancreatic necrosis infection or mortality[16]. Antibiotic abuse is a global challenge, leading to antibiotic resistance, which harms global health[17].

Fasting, gastrointestinal decompression and nutritional support: Fasting can reduce the production of digestive enzymes and inflammatory response, thereby limiting the risk of pancreatic necrosis and infection. Gastrointestinal decompression is suitable for AP patients with gastrointestinal dysfunction. For severe AP patients with abdominal compartment syndrome (ACS), decompression should be performed early to reduce mortality and infection rates[18]. As the condition improves, nutrition support should be gradually introduced, starting with clear liquids, then progressing to a low-fat, soft diet, and finally, a normal diet. This staged approach helps to avoid overstimulating the pancreas and ensure that the patient receives adequate and appropriate nutrition for recovery.

Surgical treatment: AP can cause serious complications such as pancreatic necrosis, pancreatic abscess formation and intra-abdominal infection. These conditions require surgical intervention to remove necrotic tissue, drain pus, treat infection and repair damaged tissue. The decision of surgical treatment should vary according to individual circumstances, based on the patient's specific disease status and the doctor's clinical judgment. Common surgical treatment methods are: Pancreatectomy: to treat AP by removing part or all of the pancreas[19]. The specific scope of resection depends on the degree of inflammation and the damage to the pancreas. Endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy: For biliary AP[20], interventional treatment can be performed by ERCP[21]to remove biliary stones, repair biliary obstruction, thereby eliminating the potential cause of pancreatitis, reducing the occurrence and recurrence risk of inflammation. Sphincterotomy is a surgical procedure used to treat common bile duct obstruction, biliary stricture and other diseases. By cutting or dilating the sphincter of the bile duct, bile can flow smoothly. ERCP combined with sphincterotomy is usually performed in emergency situations, to deal with acute biliary obstruction, cholangitis, biliary stones and other serious biliary diseases. However, for patients with severe gallstone pancreatitis but no cholangitis, urgent ERCP combined with sphincterotomy did not reduce the major complications or mortality compared with conservative treatment, so a conservative strategy is adopted for patients with only severe acute gallstone pancreatitis[22], and ERCP is only performed for patients with cholangitis or biliary obstruction[23]. Cholecystectomy: If AP is caused by gallstones[20,22-24], cholecystectomy can remove the gallbladder, eliminate the stones and inflammation in the gallbladder, reduce the risk of bile stasis and biliary obstruction, thereby preventing or alleviating biliary AP attacks.

Drainage therapy is an important part of AP management, especially when fluid accumulation occurs in the pancreas or surrounding tissues. Pancreatic fluid collections (PFCs) are common complications of AP, and need timely drainage to reduce inflammation and promote recovery. Here are some of the main drainage methods: Surgical drainage: In severe AP cases, surgical drainage may be needed to guide the pancreatic fluid out, remove inflammatory tissue. Usually used as a last resort, suitable for cases where other non-surgical methods are ineffective. Percutaneous drainage (PCD)[25]: Through the skin catheter, the drainage tube is inserted into the pancreas and intestine, draining the pancreatic fluid. This approach is useful in specific cases such as pancreatic pseudocyst. Studies have shown that PCD can significantly reduce the inflammatory response, accelerate the recovery of normal CRP levels, and reduce the risk of multiple organ failure[26] and surgical debridement[27]. For severe AP patients, PFC can also reduce the treatment costs of patients[28]. Transintestinal drainage (PTCD): By draining the pancreatic secretions to the intestine, reducing the pancreatic inflammation and pressure, helping to recover. This drainage can prevent complications,

reduce pancreatic tissue damage. Endoscopic retrograde cholangiopancreatography (ERCP) drainage: Endoscopic technology drains pancreatic fluid and bile, relieving pancreatic pressure. ERCP is widely used in pancreatic diseases, including cancer cell detection, etiology exploration, pancreatic duct pressure measurement, etc. However, it should be noted that ERCP complications and mortality risk cannot be ignored, especially pancreatitis and sedation-related adverse events[29-31]. Endoscopic ultrasound-guided drainage (EUS-GD): Combining endoscopy and ultrasound technology, puncturing through the gastrointestinal wall into the gallbladder or pancreas for drainage. Suitable for cases where ERCP cannot be performed, such as complex pancreatic diseases or biliary obstruction.

Pancreatic enzyme replacement therapy (PERT): In AP patients, pancreatic exocrine insufficiency (PEI) is a common phenomenon. Studies have found that more than 60% of acute pancreatitis hospitalized patients have PEI[32]. Normally, the adult pancreas secretes a large amount of digestive enzymes every day. The benefits of PERT therapy include providing nutritional support, relieving pain, promoting recovery, and preventing complications. This therapy aims to supplement the lost enzyme function of the pancreas, reduce pancreatic duct pressure, support the recovery of critically ill patients, and prevent malnutrition-related complications by ensuring proper digestion and nutrient absorption. The current pancreatic enzyme preparations include enteric-coated (such as Creon, Zenpep, etc.) and non-enteric-coated (such as Viokase) two types[33]. Enteric-coated preparations can dissolve in the duodenum, avoiding gastric acid destruction of the enzyme[34]. Increasing evidence suggests that pancreatic enzyme replacement therapy is an effective and safe method for treating PEI.

4. The latest treatment methods for acute pancreatitis

Targeted therapy: Currently, the effects of corticosteroids and antioxidants in the treatment of acute pancreatitis are still inconclusive. But emerging targeted therapies, such as using interleukin-1 receptor antagonists (such as anakinra) and protease inhibitors gabexate mesylate, show the potential of modulating inflammatory response to treat acute pancreatitis. For example, a study[35] found that nanocarrier-loaded salidroside effectively reduced local and systemic inflammation in a rat model of acute pancreatitis. Inflammatory mediator TNF-alpha is elevated in the early stage of acute pancreatitis, and its early intervention may be an effective treatment. Infliximab, a monoclonal antibody against TNF-alpha, is widely used to treat inflammatory diseases[36], and also shows potential application prospects for acute pancreatitis. Acute pancreatitis may cause systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), and studies[37] have identified the key role of inflammatory mediators such as TNF-alpha, IL-1beta, IL-6, etc. in this process. Therefore, these inflammatory mediators as new therapeutic targets, are expected to develop effective anti-inflammatory treatment methods.

Exosome therapy: Exosomes are important carriers of intercellular communication, and have important implications for the diagnosis and treatment of pancreatic diseases. These particles contain proteins, RNA, etc., and can regulate gene expression by affecting miRNA levels, thereby regulating inflammatory response, angiogenesis and cell protection after injury. Exosomes participate in various physiological and pathological processes, including biological development, genetic regulation and immune regulation. In the diagnosis of AP, exosome detection carrying miRNA shows research potential[38]. They play a key role in the treatment of AP and its complications, especially inflammation, through mechanisms such as apoptosis, immune regulation, etc[39]. For example, salidroside, a natural antioxidant and anti-inflammatory agent, has been shown to prevent acute lung injury caused by AP in mice. Compared with stem cells, exosomes are smaller, simpler, easier to produce and store, and have no risk of tumorigenesis. However, the role of

exosomes in different stages of pancreatic disease varies, and current research focuses on the functional repair and tissue remodeling signals mediated by them. The clinical application of exosomes is still in its infancy, and needs to solve problems such as separation technology, drug use methods and potential side effects. In the future, to expand the application of exosomes in AP, these challenges must be overcome, and further research is needed to identify potential defects associated with their application, especially safety and dose response[39].

5. Conclusion

In this article, we reviewed the current status and research progress of AP treatment. The literature indicates that early intervention, including intravenous fluid, fasting, analgesia and antibiotic therapy, is essential for AP treatment. However, AP treatment requires a more personalized and comprehensive approach. Based on the latest research, we focused on potential treatment strategies, such as ERCP, EUS-GD and drug therapy targeting inflammatory mediators, which showed promise in improving prognosis and survival rate. Despite this, AP treatment still faces challenges and controversies. Further research is needed to explore personalized treatment, inflammation regulation and complication prevention. For severe AP patients, intensive care and supportive treatment are still key. Future research should better understand the pathogenesis of AP, develop personalized treatment methods for specific etiologies and inflammatory pathways, while paying attention to preventing complications, improving the survival rate and quality of life of severe patients. In summary, AP treatment is a challenging field, but continuous research and exploration will improve treatment outcomes and provide more effective strategies for clinical practice.

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