

## 급성 췌장염의 치료: 영양과 항생제

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### Nutrition and Antibiotics for Acute Pancreatitis

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Acute pancreatitis is a sudden inflammatory disease that could be developed into a fatal condition. Traditional dogma was to rest the pancreas by fasting. However, evidence shows the benefits of early enteral feeding resulting in a shorter hospital stay, improved mortality, multi-organ failure, systemic infections, and the need for operative interventions. Clinicians should encourage enteral feeding as soon as possible even in severe acute pancreatitis if there are no contraindications. An immediate solid diet could be attempted. Regarding tube feeding, the nasojejunal tube did not show superiority to the nasogastric tube. Different formulas and probiotics need more investigation. Guidelines are against using prophylactic antibiotics, but Korean centers still report overuse of antibiotics. However, there is still a debate about using prophylactic antibiotics in severe acute pancreatitis. Broad-spectrum antibiotics should be initiated when an infection is suspected. In conclusion, enteral nutritional support and optimal use of antibiotics are the keys to the management of acute pancreatitis.

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## INTRODUCTION

Acute pancreatitis (AP) is a sudden inflammation of the pancreas, mostly caused by alcohol abuse and gallstone.<sup>1</sup> Majority of pancreatitis is mild accounting 80%, and 20% of patients can develop to severe necrotizing pancreatitis, which could be life-threatening. The mortality of mild pancreatitis is less than 1%. However, in case of infected necrotizing pancreatitis, mortality increases up to 43%.<sup>2</sup> Prediction and evaluation of the disease severity is the initial step for the management of AP. However, clinical course of AP is sometimes unpredictable and

differentiating patients with moderately severe to severe AP from those with mild disease severity could be difficult. Prevention and management of infection with other supportive measures is one of the keys for improving patient's outcome. The main therapy bases on aggressive hydration, pain control, nutritional support with/without antibiotics.<sup>3</sup> Herein, this article focuses on nutritional support and antibiotics for the management of AP.

## MAIN BODY

### 1. Nutrition

Away from a traditional dogma “rest the pancreas”, early enteral feeding is now recommended today.<sup>4-7</sup> In the past, people thought that pancreas would be protected by limiting enteral feeding by not stimulating exocrine pancreatic secretion. Instead of minimizing enzyme-driven inflammation and autolytic processes of the pancreas and its surrounding soft tissues, enteral starvation alters gut mucosal environment and permeability, making vulnerable to bacterial translocation. Animal studies showed that sustained enteral nutrition helps to maintain villus height and immunity leading to reduced bacterial translocation and decreased risk of the complications of pancreas necrosis and infection.<sup>8,9</sup> Paneth cell, which protects host from both commensal and pathogenic bacteria, was compromised in a mouse starvation model.<sup>10</sup> Increased bacterial translocation to mesenteric lymph nodes was also observed in the study.<sup>10</sup> Furthermore, parenteral nutrition reduces production of gut-associated lymphoid tissue cytokines giving negative impact on gut mucosal immunity.<sup>11</sup> With these experimental evidences, many studies have shown benefits of enteral feeding. A meta-analysis of eight trials concludes improved mortality (relative risk [RR] 0.5), multiple organ failure (RR 0.55), systemic infections (RR 0.39), the need for operative interventions (RR 0.46), systemic infection (RR 0.39), and local septic complications (RR 0.74) in enteral feeding group compared to parenteral feeding group.<sup>12</sup> Even though enteral feeding seems to be beneficial, nutrition strategy should be determined considering patient’s condition and severity of the disease.

#### 1) Mild acute pancreatitis

Mild AP usually resolves in several days. In the past, oral intake was limited for several days until clinical symptoms improve with normalizing amylase, lipase level. Today, if tolerated, immediate enteral feeding is recommended with avoiding parenteral nutrition.<sup>3-7</sup> Mostly, hydration is enough for patients with mild pancreatitis. Studies demonstrated shorter duration of intravenous fluid, shorter fasting days, and shorter length of hospital stay in the oral feeding group compared to fasting group in mild AP.<sup>13-15</sup>

According to initial study on enteral feeding, enteral feeding group showed significant decrease in APACH II score and C-reactive protein (CRP) level during acute phase of pancreatitis, implying that enteral feeding modulates the inflammatory and sepsis response.<sup>13</sup> In real world, patients are still fed in an increasing manner in many centers; clear liquid, low-fat soft diet, low fat solid diet.<sup>16</sup> However, immediate solid diet was found out to be safe (no difference in pain relapse) and can reduce the length of hospital stay.<sup>16</sup>

#### 2) Severe acute pancreatitis

Severe AP is systemic inflammatory response syndrome (SIRS), which increases basal metabolic rate and energy consumption leading to a catabolic state.<sup>17</sup> Catabolic stress with nutritional deficiency give negative clinical outcome, especially in malnourished alcoholics. Therefore, nutrition is much more important in severe AP than in mild AP. Guidelines recommend enteral feeding in severe AP, possibly within 48 hours of admission.<sup>3-7,18</sup> A meta-analysis performed subgroup analysis with studies with severe AP, and enteral feeding showed much better outcome in mortality (RR 0.18) compared to that of all patients with AP (RR 0.5).<sup>12</sup> Other meta-analyses of studies for severe AP have shown clinical benefits of enteral feeding over parenteral feeding, e.g., reducing infectious complications and mortality.<sup>19,20</sup> These results are important and oral feeding should be started as soon as possible. However, in patients with severe AP, conditions often do not allow oral feeding because of ileus, organ failure and other metabolic problems. For those who are unable to tolerate oral intake, early nutritional support should be considered within the first 24-72 hours by nasogastric or nasojejunal tube.<sup>18</sup> It is quite clear that enteral feeding shows better clinical outcomes compared to parenteral feeding. However, the timing of feeding remains controversial.<sup>15</sup> Bakker et al.<sup>21</sup> conducted a randomized trial comparing early nasoenteric tube feeding and an oral diet at 72 hours after presentation with severe AP. Patients were randomly assigned either to early group (nasoenteric tube feeding within 24 hours) or to on-demand group (diet initiated 72 hours after presentation), and early group did not show the superiority in reducing infection or mortality.<sup>21</sup>

### 3) Nasogastric or nasojejunal tube feeding

Nasojejunal tube may have merits in preventing aspiration pneumonia and resting pancreas, but a meta-analysis was not able to conclude any superiority or inferiority between nasogastric and nasojejunal feeding.<sup>22</sup> Considering the merits of nasogastric tube (easier placement, cheaper cost), nasojejunal tube should be used for patients with gastric outlet obstruction.<sup>7,18</sup>

### 4) Formula and probiotics

ESPEN guidelines recommend standard polymeric diet in patients with AP.<sup>23</sup> Immuno-enhanced formulations, such as formula containing glutamine, omega-3 fatty acids, nucleotides, fibre-enhanced formulations have been tried, but they did not show clear clinical benefits.<sup>24</sup> For prevention of bacterial translocation from the intestinal tract to the blood stream and necrotic tissue, probiotics were tried as it could stabilize intestinal barrier. However, Besselink et al.'s randomized controlled study with probiotic prophylaxis for severe AP did not reduce infectious complications.<sup>19</sup> On the other hand, surgical intervention, bowel ischemia and mortality was higher in probiotics group. Meta-analysis also did not show no benefit of probiotics in AP.<sup>25</sup> Therefore, guidelines are against using probiotics yet.<sup>5,7</sup>

## 2. Antibiotics

As AP is associated with a SIRS, especially in the early phase of the disease, patients present with fever, tachypnea, tachycardia and leukocytosis. SIRS could be mistaken as infection and can lead to unnecessary use of antibiotics. One study showed 62% of all patient with AP showed SIRS on the day of admission.<sup>26</sup> As infection largely determines prognosis of a patient, there is high chance of overuse of AP. A global survey showed global trend of antibiotics overuse, and Korean centers in the study reported that over 50% of patients used antibiotics among patients with AP. The survey reported 90% of antibiotics therapy is started in the first 3 days.<sup>27</sup>

### 1) Prophylactic antibiotic

Guidelines do not recommend routine use of prophylactic antibiotics as they did not decrease in mortality.<sup>4-6</sup> Several RCTs

have shown no benefit of prophylactic antibiotics for preventing infection, mortality.<sup>28-30</sup> No difference of mortality was consistently reported by meta-analysis of RCTs.<sup>31-33</sup> Poor penetration to necrosis is thought to be one of the reasons of the result, and routine prophylactic antibiotics may lead to infection by multidrug resistance bacteria or fungus with elevation of medical cost. However, there are some reports favoring prophylactic antibiotics in severe pancreatitis. Japanese guideline recommend using prophylactic wide-spectrum antibiotics for severe AP within 72 hours of onset.<sup>6</sup> Their meta-analysis team focused on timing of antibiotics administration, and trials with early administration (72 hours after onset of symptoms or 48 hours after admission) trials were included. Antibiotics group showed better result in mortality rates (OR 0.48; 95% confidence interval [CI] 0.25-0.94) and infection of pancreatic necrosis (OR 0.55; 95% CI 0.33-0.92).<sup>34</sup> UK guideline recommend considering prophylactic antibiotics in patients with necrosis more than 30% as the risk of infected necrosis is very small when necrosis is less than 30%.<sup>4</sup>

Even though prophylactic antibiotics is not generally recommended, broad spectrum antibiotic should be initiated when infection is suspicious. Image (gas in a pancreatic or peripancreatic collection), laboratory examination (worsening white blood cell [WBC], CRP, procalcitonin), clinical symptom/sign (sustained fever, persistent unwellness, or clinical deterioration) are suggested.<sup>18</sup> However, WBC or CRP should not be sole factor to decide to use antibiotics.<sup>27</sup> As many of these factors can be seen in the setting of SIRS, distinguishing infected necrosis could be difficult based on clinical parameters alone.

### 2) Which antibiotics should be used?

For selection of antibiotics, penetration to pancreatic tissue as well as necrotic tissue and specific activity against the common bacteria for pancreatic infection should be considered. Major organisms are gastrointestinal Gram-negative bacteria (*E. coli*, *Pseudomonas*, *Proteus*, *Klebsiella*). Traditionally, carbapenem and quinolone have been used for acute pancreatitis. The 3rd or higher generation cephalosporine also seems to show good penetration to the pancreatic tissue.<sup>35,36</sup>

## CONCLUSIONS

Nutritional optimization is important and if possible, immediate enteral feeding is recommended. Prophylactic antibiotics could not be generally recommended, but clinician should not hesitate to use antibiotics if there is any clinical clue of infection.

## 요약

급성 췌장염은 담석, 음주 등의 원인으로 발생하는 급성 염증성 질환이다. 약 80%에서는 췌장에만 염증이 생기는 경증 췌장염으로 그치나, 약 20%의 환자에서는 중증 괴사성 췌장염으로 발전하고, 보고에 따라 사망률이 43%에 이른다. 이에 따라 초기의 집중적인 치료는 매우 중요하다. 본고에서는 급성 췌장염의 치료 중 영양과 항생제의 사용에 대해 살펴보고자 하였다. 전통적으로 급성 췌장염은 금식으로 췌장을 쉬게 한다는 개념으로 한 치료가 강조되었고, 이와 함께 대량 수액 공급, 통증 조절, 영양 공급, 적절한 항생제 치료가 주로 이루어졌다. 그러나 최근 초기에 경장 영양을 시작하는 것이 입원 기간 단축, 다발성 장기 부전, 전신 감염, 수술적 치료 필요성을 개선시키고 사망률을 개선시킨다는 것이 여러 연구들을 통해 입증되었다. 따라서 금기사항만 없다면 가급적 초기에 경장 영양을 시키는 것이 장려된다. 또한 무작위 대조군 연구들에 따르면 예방적 항생제가 감염을 예방하거나 사망률을 감소시키는 것에 도움이 되지 않고 오히려 항생제 내성을 유발하고 의료비 지출이 높아지므로 예방적 항생제 사용을 권장하지 않고 있다. 하지만 중증 급성 췌장염에서는 예방적 항생제를 쓰는 것에 대해 여전히 논란이 되고 있고 감염이 의심될 때에는 광범위 항생제를 초기에 쓰는 것이 필요하다. 결론적으로 급성 췌장염의 치료에 있어 전통적으로 행해 왔던 금식보다는 초기에 경장 영양을 시작하고 항생제는 적절히 사용하는 것이 중요하다.

국문 색인: 췌장염; 영양; 항생제

## Conflicts of Interest

The authors have no conflicts to disclose.

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