

# Systemic Review for The Effectiveness of Current Conservative Treatment in Necrotizing Pancreatitis

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## 괴사성 췌장염에서 보존적 치료의 효용성에 대한 고찰

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The standard treatment of pancreatic necrosis has been surgical necrosectomy. There has been debate on whether early surgical intervention can reduced by infected pancreatic necrosis (IPN). Early emergency laparotomy and multiple organ failure remain associated with high mortality. However, reports have presented during the last 10 years of survival of severe acute pancreatitis with medical management. Large and multicenter study showed that about two thirds of patients with necrotizing pancreatitis can be treated conservatively with relatively low mortality. Patients with IPN benefit from postponing intervention and minimal invasive treatment. We reviewed 4 literatures including 2 Korean institute researched reports concerning non-surgical, conservative treatments of necrotizing pancreatitis including IPN. Large and multicenter study showed that about two thirds of patients with necrotizing pancreatitis can be treated conservatively with relatively low mortality.

**Key Words:** Acute pancreatitis, Infection, Necrosis, Treatment

## BACKGROUND & AIMS

Severe necrotizing pancreatitis, especially in IPN is associated with a high rate of complications and mortality. The standard treatment is open necrosectomy. The surgical view that has been in mode for many years is that the confirmation of IPN should lead to immediate surgical debridement including pancreatectomy. It is said that the failure to do surgery will lead to very high mortality. However, reports have presented during the last 10 years of survival

of severe acute pancreatitis with medical management. Medical managements such as nutritional support intensive care, and combination of antibiotics with or without drainage of the infected fluid has been shown to be effective for patient with IPN. We performed a current systemic review and meta-analysis studies related to conservative management for necrotizing pancreatitis including IPN.

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## PATIENTS AND METHODS

We reviewed 4 literatures searched reports concerning non-surgical, conservative treatments of necrotizing pancreatitis from Venigalla pratap mouli, et al.,<sup>1</sup> Hjalmar C, et al.,<sup>2</sup> Jun kyu Lee, et al.,<sup>3</sup> and Ju Hyung Song, et al.,<sup>4</sup> Venigalla Pratap Mouli, et al., performed a literature search for primary conservative treatment 324 patients without necrosectomy, for consecutive patients with IPN.<sup>1</sup> Hjalmar C, et al. collected data from 639 consecutive patients with necrotic pancreatitis.<sup>2</sup> Jun Kyu Lee, et al., studied to evaluate the efficacy of nonsurgical treatment for 31 patients diagnosed as having IPN complication. Ju Hyung Song, et al., conducted the study to evaluate the outcomes of early intensive non-surgical treatments in 71 patients with acute severe necrotizing pancreatitis.<sup>4</sup>

## RESULTS

There was significant heterogeneity in results among the studies. Conservative management was successful for 64% of patients, mortality was 12%, 26% of patients required necrosectomy or additional surgery for complication.<sup>1</sup>

Treatment was conservative in 62%, with 7% mortality. An intervention was performed 38%, with 27% mortality. Overall mortality was 15%. Organ failure occurred in 38%, with 35% mortality.<sup>2</sup> The success rate of medical treatment group in IPN was 79%. The mortality rate of medical treatment group and surgical treatment group was 5% and 50%.<sup>4</sup>

## CONCLUSIONS

Intensive non-surgical treatment is very effective and safe should be considered as an initial treatment modality for patient with IPN.<sup>3,4</sup>

Conservative management without necrosectomy is successful approach for 62% to 64% of patients with IPN. This approach has low mortality and prevents surgical necrosectomy. In patients with infected necrosis, delayed intervention and catheter drainage as first treatment improves outcome.<sup>1,2</sup>

The clinical course of acute pancreatitis is mostly mild one usually recovered within 3 to 5 days.<sup>5</sup> Acute pancreatitis is complicated by necrosis in approximately 20% patients.<sup>6,7</sup> There are two major forms of acute pancreatitis: interstitial and necrotizing. Acute necrotizing pancreatitis usually runs a severe course and is the cause of most of the morbidity and mortality.<sup>7</sup> The extent and infection of pancreatic necrosis correlate with the development of organ failure and mortality in acute pancreatitis.<sup>8,9</sup> Interventions in the first phase are relatively contraindicated, although some patients require an emergency laparotomy for complications such as abdominal compartment syndrome or bowel ischemia.<sup>10</sup> It has been suggested that approximately that half of the deaths from necrotizing pancreatitis are caused by multiple organ failure in the early phase.<sup>11,12</sup> In the later phase of the disease (ie, after 1-2 weeks), systemic inflammation often regresses and infected necrosis occurs in about 30% of patients with necrotizing pancreatitis.<sup>13,14</sup> IPN is the cause of most of the late mortality during the course of acute pancreatitis. Although conservative treatment is recommended for sterile necrosis, surgical necrosectomy has generally been considered the standard

of care for IPN according to various practice guidelines.<sup>15-17</sup> Immediate surgery is currently recommended for the treatment of IPN. However, there has been debate on whether early surgical intervention can reduce complications or mortality caused by IPN. Treatment of necrotizing pancreatitis has changed considerably over the years. First, the indication for intervention has shifted. Whereas historically most patients with sterile necrosis underwent necrosectomy, it is now accepted that sterile necrosis should largely be managed conservatively and that the main indication for interventions infected necrosis.<sup>10,15,18,19</sup> Second the timing of intervention has changed. Necrosectomy was once performed at a very early stage,<sup>20</sup> but now it is believed that intervention should be delayed to approximately 3 to 4 weeks after onset of disease.<sup>15,21,22</sup> Nonsurgical methods are included percutaneous drainage (PCD) or endoscopic drainage (ED), for the treatment of IPN whenever needed.

## STUDY DESIGN AND INCLUSION CRITERIA

Conservative treatment was defined as supportive treatment, including care in an intensive care unit and antimicrobial therapy with or without percutaneous drainage (PCD) and endoscopic drainage (ED) but without any form of necrosectomy. The inclusion criteria was signs of pancreatic necrosis and/or peripancreatic necrosis on contrast-enhanced computed tomography (CECT). IPN was confirmed identification of an offending organism by fine needle aspiration (FNA) from the necrotic area or presence of free gas in the pancreas on CECT. The severity of acute pancreatitis was assessed using CT severity index<sup>23</sup> and Ranson Criteria.<sup>24</sup> The organ failure was

defined as follows: (1) pulmonary; Pao<sub>2</sub> less than 60 mmHg at room air; (2) renal, serum creatinine level more than 3.0 mg/dL; (3) cardiovascular, systolic blood pressure less than 80 mmHg over 15 minutes; (4) liver, total bilirubin level more than 6.0 mg/dL; (5) coagulation, platelet count less than 50,000/ $\mu$ L; and (6) neurologic Glasgow Coma Scale less than 10. Multiple organ failure defined as the presence of 2 or more organ failure. The diagnostic criteria for a systemic inflammatory response syndrome (SIRS) cited in the results were as follows: when 2 or more of the following conditions are met: temperature of less than 36C or more than 38C, heart rate of more than 90 beats per minute, respiratory rate of more than 20 breaths per minute, and white blood cell count of less than 400/ $\mu$ L or more than 12,000/ $\mu$ L.<sup>17,25,26</sup>

## DISCUSSION

The standard treatment of pancreatic necrosis has been surgical necrosectomy. IPN is a potentially life threatening complication of acute pancreatitis. Patients with pancreatic parenchymal necrosis had significantly higher mortality than patients with peripancreatic necrosis alone (20% vs 9%).<sup>2</sup> Many studies confirmed conservative treatment without necrosectomy became the standard recommendation for treating patients with sterile necrotic pancreatitis over the next 2 decades.<sup>5</sup> IPN has, however, been considered an absolute indication for necrosectomy for many reasons: (1) surgical principles dictate removal of the solid infected material, (2) antibiotics do not penetrate well into pancreatic necrotic tissue, and (3) such patients are quite sick, requiring early intervention to control sepsis. Treatment can be conservative in about two-thirds of patients with

necrotizing pancreatitis.<sup>2</sup> In case of IPN, one-third of patients can be successfully treated with percutaneous (or endoscopic transluminal) catheter drainage and do not need any form of necrosectomy. If catheter drainage is unsuccessful, minimally invasive retroperitoneal and endoscopic transluminal necrosectomy are safe and feasible techniques.<sup>2</sup> Johnson and Blum, et al., confirmed that approximately half of the patients with necrotizing pancreatitis who die have sterile necrosis. Mortality in these patients is almost exclusively caused by multiple organ failure in first week.<sup>11,12</sup> Organ failure in the first week was significantly higher than in patients with organ failure occurring after the first week (41% vs 28%).<sup>2</sup> This supports the theory that organ failure early in the course of acute pancreatitis, which is associated with systemic release of cytokines and systemic response syndrome, is a different clinical entity than organ failure as a result of sepsis from infected necrosis at a later stage. More than one-third of patients with necrotizing pancreatitis underwent an intervention, which was associated with 27% mortality.<sup>2</sup> The results of the meta-analysis show that indeed a strategy of primary conservative treatment is not only feasible but also successful in treating patients with IPN.<sup>1</sup> Lee, et al., showed excellent results with a very low mortality of 3.2%, which could be due to relatively stable patients in their series.<sup>27</sup> Another Korean study showed a high success rate of 78.9% with conservative treatment.<sup>28</sup> Overall, nearly two-thirds of the patients with IPN improved with conservative management alone, about one-fourth required additional surgical procedures for necrosectomy or for complications related to the percutaneous drainage, and the mortality was approximately 12%.<sup>1</sup> An important argument is that percutaneous drainage

is an intervention and thus may not be considered as part of conservative treatment. However, Venigal, et al., included percutaneous drainage in conservative treatment because (1) most studies included percutaneous drainage in their conservative treatment protocol and (2) the primary goal of this analysis was to assess the effectiveness of nonsurgical versus surgical management of IPN.<sup>1</sup> Van, et al., advise that all patients with suspected or confirmed infected necrosis are treated with percutaneous or endoscopic catheter drainage first.<sup>29</sup> The administration of proper antibiotics and early adequate drainage with through saline irrigation can delay the need for surgery and even eliminate the need for surgery in some patients.<sup>3</sup> In a randomized controlled trial, complications developed in 69% of patients who underwent open surgical necrosectomy.<sup>29</sup> It is quite possible that many patients with presumed sterile necrosis might have had IPN, because infection was ruled out in most cases by fine needle aspiration. Current evidence suggests the conservative treatment might be successful for IPN as well. Multiple factors possibly contribute to the success of conservative management of patients with IPN. These include organ support, the use of effective new generation antibiotics, aggressive nutritional support, and timely percutaneous drainage.

In conclusion, large and multicenter study showed that about two thirds of patients with necrotizing pancreatitis can be treated conservatively with relatively low mortality. Early emergency laparotomy and multiple organ failure, however remain associated with high mortality. Patients with infected necrosis benefit from postponing intervention and minimally invasive techniques. One-third of these patients can be treated with percutaneous or endoscopic transluminal catheter drainage only and do not require

necrosectomy.

## REFERENCES

1. Mouli VP, Sreenivas V, Garg PK. Efficacy of Conservative Treatment, Without Necrosectomy, for Infected Pancreatic Necrosis: A Systemic Review and Meta-analysis. *Gastroenterology* 2013;144:333-40.
2. Van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al. A Conservative and Minimally Invasive Approach to Necrotizing Pancreatitis Improves Outcome. *Gastroenterology* 2011;141:1254-63.
3. Lee JK, Kwak KK, Park JK, Yoon WJ, Lee SH, Ryu JK, et al. The efficacy of nonsurgical treatment of infected pancreatic necrosis. *Pancreas* 2007;34:399-404.
4. Song JH, Seo DW, Byun SW, Koo DH, Bae JH, Lee SS, et al. Outcome of intensive medical treatment in patients with infected severe necrotizing pancreatitis. *Korean J Gastroenterol* 2006;48:337-43.
5. Werner J, Feuerbach S, Uhl W, Buchler MW. Management of acute pancreatitis: from surgery to interventional intensive care. *Gut* 2005;54:426-36.
6. Beger HG, Rau B, Mayer J, Pralle U. Natural course of acute pancreatitis. *World J Surg* 1997;21:130-5.
7. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993;128:586-90.
8. Garg PK, Madan K, Pande GK, Khanna S, Sathyanarayan G, Bohidar NP, et al. Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. *Clin Gastroenterol Hepatol* 2005;3:159-66.
9. Isenmann R, Rau B, Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. *Br J Surg* 1999;86:1020-4.
10. Nathens AB, Curtis JR, Beale RJ, Cook DJ, Moreno RP, Romand JA, et al. Management of the critically ill patient with severe acute pancreatitis. *Crit Care Med* 2004;32:2524-36.
11. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* 2004;53:1340-4.
12. Blum T, Maisonneuve P, Lowenfels AB, Lankisch PG. Fatal outcome in acute pancreatitis: Its occurrence and early prediction. *pancreatology* 2001;1:237-41.
13. Besselink MG, van Santvoort HC, Boermeester MA, Nieuwenhuijs VB, van Goor H, Dejong CH, et al. Timing and impact of infections in acute pancreatitis. *Br J Surg* 2009;96:267-73.
14. Banks PA, Freeman ML. Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006;101:2379-400.
15. Gurusamy KS, Farouk M, Tweedie JH. UK guidelines for the management of acute pancreatitis: is it time to change? *Gut* 2005;54:1344-5.
16. Werner J, Feuerbach S, Uhl W, Büchler MW. Management of acute pancreatitis: from surgery to interventional intensive care. *Gut* 2005;54:426-36.
17. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, et al. IAP guidelines for surgical management of acute pancreatitis. *Pancreatology* 2002;2:565-73.
18. Forsmark CE, Baillie J; AGA Institute Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA institute technical review on acute pancreatitis. *Gastroenterology* 2007;132:2022-44.
19. Büchler MW, Gloor B, Müller CA, Friess H, Seiler CA, Uhl W. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. *Ann Surg* 2000;232:619-26.
20. Mier J, León EL, Castillo A, Robledo F, Blanco R. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg* 1997;173:71-5.
21. Fernández-del Castillo C, Rattner DW, Makary MA, Mostafavi A, McGrath D, Warshaw AL. Debridement and closed packing for the treatment of necrotizing pancreatitis. *Ann Surg* 1998;228:676-84.
22. Besselink MG, Verwer TJ, Schoenmaeckers EJ, Buskens E, Ridwan BU, Visser MR, et al. Timing of surgical intervention in necrotizing pancreatitis. *Arch Surg* 2007;142:1194-201.
23. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis ; value of CT in establishing prognosis. *Radiology* 1990;174:331-6.
24. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974;139:69-81.
25. United Kingdom guidelines for the management of acute pancreatitis. British Society of Gastroenterology. *Gut* 1998;42:S1-13.
26. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines

- for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest 1992;101:1644-55.
27. Lee JK, Kwak KK, Park JK, Yoon WJ, Lee SH, Ryu JK, et al. The efficacy of nonsurgical treatment of infected pancreatic necrosis. *Pancreas* 2007;34: 399-404.
28. Song JH, Seo DW, Byun SW, Koo DH, Bae JH, Lee SS, et al. Outcome of intensive medical treatments in patients with infected severe necrotizing pancreatitis. *Korean J Gastroenterol* 2006;48:337-43.
29. Van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010;362:1491-502.

### Peer Reviewers' Commentary

Large and multicenter study showed that about two thirds of patients with necrotizing pancreatitis can be treated conservatively with relatively low mortality. Early emergency laparotomy and multiple-organ failure, however remain associated with high mortality. Patients with infected necrosis benefit from postponing intervention and minimally invasive techniques. One-third of these patients can be treated with percutaneous. In this review, effectiveness of current conservative treatment in necrotizing pancreatitis to make it easier to understand the summary.

(Comment: Editorial Committee)