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**Invasive intervention timing for infected necrotizing pancreatitis: late invasive intervention is not late for collection**

Invasive intervention timing for INP

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## **Abstract**

With the advance of invasive interventions, the treatment model for infected necrotizing pancreatitis has shifted from open surgery to the step-up minimally invasive treatment. Late intervention, originating from the open surgery era, has been questioned in the minimally invasive period. With the emergence of new high-quality evidence about the timing for intervention, it seems to be increasingly apparent that, even in the age of minimal invasiveness, "late intervention" waiting for the necrotic collections to be encapsulated is still necessary. This opinion review mainly discusses the intervention timing for infected necrotizing pancreatitis.

**Key Words:** Pancreatitis, Walled-off Necrosis, Minimally Invasive Surgery, Endoscopic Drainage, Endoscopic Gastric Fenestration

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**Core Tip:** Infected necrotizing pancreatitis is a potentially lethal disease that should be identified and managed early. For patients who can be stabilized with antibiotics and supportive care, the invasive treatment, either endoscopic or percutaneous approach, should be delayed for at least four weeks. While patients whose infection cannot be controlled by medication alone may need percutaneous drainage first in 48-72 h, followed by minimally invasive surgery (if necessary). Endoscopic gastric fenestration may be performed in selected patients. This innovative alternative intervention should also be postponed to more than four weeks, waiting for the necrosis to mature and the capsular lesions to fuse with the gastric wall.

## **INTRODUCTION**

Acute pancreatitis is one of the most common pancreatic diseases. According to the revised Atlanta classification<sup>[1]</sup>, acute pancreatitis is categorized into interstitial edematous and necrotizing pancreatitis. The prognosis of acute edematous pancreatitis is usually favorable. However, acute necrotizing pancreatitis (ANP) is potentially lethal since it has a high ratio of complications. Acute necrotic collection (ANC) and walled-off necrosis (WON) are two main local complications of ANP, arising from pancreatic and/or peripancreatic necrosis in the early and late phases, respectively. During the evolution of the disease, the necrosis may remain sterile or become infected. Once infection occurs, as the liquefaction of the infected pancreatic necrosis progresses, there may be an increasing amount of suppuration, which was described as "pancreatic abscess" in the original Atlanta classification and some older literature. Since the collections usually contain solid necrotic tissue, the term "pancreatic abscess" was confusing and was gradually deprecated.

Currently, "infected necrotizing pancreatitis (INP)" has been preferred to describe ANP with infection. It is more common in severe acute pancreatitis (SAP) and poses a considerable threat with a mortality of up to 30-39%<sup>[2]</sup>. The treatment of INP is challenging and usually needs a multidisciplinary team to provide optimal management. Besides, invasive treatment is generally unavoidable. With the advancement of minimally invasive treatment of INP, the therapeutic algorithm has shifted from open surgery to <sup>2</sup> minimally invasive techniques, including percutaneous catheter drainage, per-oral endoscopic drainage or necrosectomy, video-assisted retroperitoneal debridement (VARD), etc. Meanwhile, the invasive intervention timing has been arousing an extensive debate as treatment approaches transform in the minimal invasion era.

Recently, we published a mini-review about pancreatic and peripancreatic collections of acute pancreatitis, in which we mainly discussed treatment approaches <sup>[3]</sup>. We did not elaborate on the timing for invasive intervention due to space limitations. Another reason was that the results of the POINTER trial<sup>[4]</sup> had not been published at that time, we did not have direct evidence about this issue, even though we had presumed that

the late intervention might be better based on our limited experience. According to the POINTER trial<sup>[5]</sup>, earlier studies, and clinical experiences, we have more confidence in late intervention for INP.

## **1. DIAGNOSIS OF INFECTED NECROTIZING PANCREATITIS**

### **1. Diagnosis of infected necrotizing pancreatitis**

In ANP, necrosis may involve the pancreatic parenchyma and/or peripancreatic tissues. The pancreatic parenchyma necrosis usually presents as a focal or diffuse area with no enhancement in the arterial and early venous phase. The peripancreatic necrosis is commonly located in the retroperitoneum and lesser sac, with heterogeneous and ill-defined regions. Both magnetic resonance imaging (MRI) and contrast-enhanced computer tomography (CECT) have a good capability in evaluating the presence and extent of pancreatic and/or peripancreatic necrosis. However, due to the characteristics of short scan duration, accurate severity evaluation, robust reproducibility, and widespread usage, CECT is recommended as the first-line imaging modality for assessing necrosis in ANP<sup>[6]</sup>. The best timing of execution of CECT is at least 72 h after symptom onset, as necrosis may be underestimated or missed due to premature assessment.

After necrosis has been evaluated, INP should be suspected if patients with systemic inflammatory response syndrome (SIRS) improve but suddenly deteriorate, the SIRS does not improve after two weeks of treatment, or there is evidence of pancreatic peripancreatic gas configurations. Increased serum procalcitonin (PCT) may consolidate the suspicion of infection, while a positive result on Gram stain or culture can diagnose the INP. Nevertheless, the obtaining of sampling, usually by applying fine-needle aspiration (FNA) guided by ultrasound or CT, is invasive. Additionally, the potential contamination and the probability of false-negative and false-positive results of this technique hamper it as a common approach to confirming INP<sup>[6]</sup>. Therefore, empirical broad-spectrum antibiotics (e.g., carbapenems, quinolones, *etc.*) can be used as a diagnostic treatment for suspected cases of INP<sup>[7]</sup>. For patients with clinical

deterioration after empirical antibiotic therapy, FNA samples are recommended to be tested to identify the infection and guide the adjustment of antibiotics.

## **2. Timing for percutaneous drainage and minimally invasive surgery**

As minimally invasive intervention and related clinical studies emerge, the standard treatment of INP has undergone a paradigm shift. The milestone PANTER trial, published in 2010, showed <sup>3</sup> that the minimally invasive step-up approach reduced the rate of major complications or mortality among patients with INP compared to traditional standard open necrosectomy<sup>[8]</sup>, which established the status of the minimally invasive step-up approach as a priority treatment. In this trial, 93% of patients in the step-up approach group received percutaneous catheter drainage as the first step. Furthermore, as shown in the POINTER trial, the postponed-drainage strategy indicated fewer invasive interventions than the immediate-drainage strategy without increasing the incidence of complications. Therefore, whenever possible, the percutaneous drainage should be postponed to about four weeks after the onset of the disease. Moreover, 39% of patients were spared invasive drainage or necrosectomy procedure with this strategy<sup>[5]</sup>.

However, it is not always appropriate to postpone the intervention in clinical practice since some patients suffer serious infections that cannot be controlled by medication alone; they usually demonstrate new-onset organ failure on the basis of SIRS or present with persistent organ failure and even aggravation of pre-existing organ failure. For these patients, early invasive drainage should be planned. Usually, after an attempt at antibiotic treatment for the first 48-72 h, we would prefer percutaneous drainage next because this approach is comparatively handy and can provide rapid source control in most infectious lesions. For adequate drainage, if necessary, the combination of percutaneous drainage and endoscopic drainage can also be considered. Meanwhile, FNA could be done before the indwelling of a drainage catheter to gather a sample, which may provide the details on the infection and the antibiotic susceptibility results. If there is no clinical improvement 48-72 h after the first drainage, another catheter

drainage or expanded drainage channel should be constructed. If patients do not show clinical improvement after an additional 48-72 h, minimally invasive surgery, for instance, VARD, should be considered, irrespective of whether the intervention time has exceeded four weeks. If there is clinical improvement, minimally invasive surgery could be postponed until the necrosis has substantially or entirely encapsulated.

### **3. Timing for endoscopic drainage and necrosectomy**

In 2012, the PENGUIN trial demonstrated that endoscopic drainage and subsequent necrosectomy (if necessary) reduced the postprocedural proinflammatory response and the composite clinical endpoint compared with percutaneous drainage and subsequent VARD or laparotomy (if necessary) in patients with INP<sup>[9]</sup>. Despite a small sample size, this was the first randomized controlled trial (RCT) comparing two minimally invasive procedures. Then, another RCT, the TENSION trial with a larger sample size, was published in 2018. Although this trial did not verify <sup>1</sup> that the endoscopic step-up approach was superior to the surgical step-up approach in reducing major complications or deaths, it demonstrated that the endoscopic step-up approach had a better effect in reducing the incidence of pancreatic fistula and shortening hospital stay<sup>[10]</sup>. The contemporaneous MISER trial also proved the superiority of the endoscopic approach in reducing fistulas<sup>[11]</sup>. Meta-analyses based on the RCTs or the other clinical cohort studies confirmed these conclusions<sup>[12-14]</sup>. Therefore, guidelines recommended the endoscopic step-up approach as a preferred treatment for endoscopically reachable lesions<sup>[7]</sup>.

If patients maintain improvement after antibiotics and other supportive care, then the timing for endoscopic drainage is also recommended to postpone until four or more weeks after initial presentation. As we have mentioned above, the POINTER trial, in which 56% of immediate drainage cases and 67% of postponed drainage cases were intervened with an endoscopic approach, did not show the benefit of early intervention. Besides, compared to the standard timing of endoscopic intervention ( $\geq 4$  wk) in patients with necrotizing pancreatitis, a retrospective study showed that early endoscopic

intervention (<4 wk) had a worse outcome in terms of median hospital days, ICU days, need for rescue open necrosectomy, and the mortality<sup>[15]</sup>. Another matched case-control study also showed that the total duration of therapy was longer for early intervention compared with the control group<sup>[16]</sup>. Moreover, late intervention is related to fewer invasive interventions. For instance, 39% of patients in the postponed group in the POINTER trial <sup>5</sup> were treated conservatively with antibiotics and did not require any invasive drainage. Additionally, for patients in the TENSION trial who indicated invasive intervention, under the premise of late invasive intervention (more than 4 wk after the onset of symptoms), 47% of them only need drainage and were exempt from necrosectomy. We list in Table 1 the major RCTs guiding the invasive intervention strategies for INP toward a better-supported recommendation for late endoscopic intervention. These results were consistent with our limited experience, and we usually do not hastily perform the endoscopic drainage in clinical practice until the lesions are encapsulated and the necrotic tissues are partially liquefied. As with the evidence discussed above, the late intervention which usually occurred more than four weeks after the onset of symptoms may have a better drainage outcome. However, in some cases of INP, despite the most outstanding support, the infection may still cause clinical deterioration, and require invasive intervention earlier. In this situation, we usually prefer percutaneous drainage, as discussed above, reserving endoscopic drainage for those who lack an ideal drainage path or have poor percutaneous drainage effects.

For endoscopic drainage, the most used stents include plastic stents and metal stents. Traditionally, to minimize migration risk, plastic stents with double pigtails have been the most used in drainage. As introduced in the TENSION trial, two 7 French double pigtail stents and an 8.5 French nasocystic catheter were used as a combination for drainage. Due to their small diameter, plastic stents are prone to occlusion during the drainage process, making them more suitable for INP with more liquid and less solid necrotic tissue. When the fluid was wholly drained or the stents were blocked, the plastic stents should be opportunely removed. Owing to the larger luminal diameter, metal stent drainage is more effective in patients with INP. Nevertheless, one of its

limitations is stent migration. As a result, various metal stents with anti-migration functions have been introduced in recent years. Among them, the most striking one is lumen-apposing metal stent (LAMS). Compared with the plastic stent, LAMS is related to a shorter procedure duration but a higher stent-related adverse event risk<sup>[17]</sup>, including LAMS buried under gastric mucosal, pseudoaneurysms bleeding, and obstructive jaundice. Most of them occurred in patients whose LAMS had been placed for more than three weeks<sup>[17]</sup>. A retrospective study also observed that patients with LAMS had a higher risk of pseudoaneurysm bleeding<sup>[18]</sup>. Therefore, it is crucial to retrieve LAMS timely after the drainage purpose is achieved. Currently, a CT scan in 3 wk is recommended to evaluate the drainage effect followed by LAMS removal to minimize the adverse events<sup>[17]</sup>.

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To avoid stent-related complications, we explored endoscopic gastric fenestration (EGF) as an innovative alternative intervention for infected WON<sup>[19]</sup>. First, endoscopic submucosal dissection (ESD) achieved initial fenestration between the stomach and the WON lesion. Then, under the guidance of endoscopic ultrasound (EUS) and the spatial direction of WON, the fenestration was suitably enlarged to 1.5-3 cm to allow efficient drainage and direct endoscopic necrosectomy. One of the greatest advantages of the EGF is the avoidance of stents and their potential complications. This approach is not suitable for all WON, since its prerequisite is the fusion of WON with its closely connected stomach wall, which can present as mucosal inflammation such as edema and erosion in the direct endoscopic view and unnormal combined thickness without distinct layers in the EUS view. Therefore, late intervention waiting for the maturity of INP and the fusion of the encapsulated lesion with the gastric wall is also necessary for the EGF.

## **CONCLUSION**

The endoscopic step-up approach has been recommended as the first-line treatment for patients with INP. With the results of published studies (especially the POINTER trial) and our limited experiences, the late invasive intervention is not late for INPs. In

contrast, this delayed invasive intervention strategy may avert the need for invasive intervention in around one-third of patients with INP. In addition, patients with late invasive intervention strategies may have the chance for an innovative EGF treatment, thereby avoiding stents and the related complications.

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