

Timing, approach, and treatment strategies for infected pancreatic necrosis: a narrative review

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Pancreatic necrosis occurs in approximately 15% to 20% of patients with acute pancreatitis (AP); 1/3 of patients are diagnosed with infected pancreatic necrosis (IPN), which has a mortality rate of 30%. It is the chief reason for the second “death peak” of AP patients in the later stage of the disease.^[1] As one of the most vital treatment methods for IPN, pancreatic necrosectomy has developed rapidly in the past 30 years, including improvements and breakthroughs in surgical timing, approach, and strategies, and a significant reduction in postoperative mortality from the initial 30% to 40%. In particular, with the innovation of laparoscopic and endoscopic techniques, pancreatic surgeons have more choices in the face of IPN. Currently, how to optimize treatment and maximize the benefits for IPN patients has become a topic of great concern and controversy in the treatment of IPN.

Database search strategy

We conducted a systematic literature search using the PubMed and Web of Science databases. The following keywords were selected: acute pancreatitis, infected pancreatic necrosis, treatment, necrosectomy, drainage, step-up, laparoscopic necrosectomy, and endoscopic necrosectomy. We selected only English language and full-text articles. All available studies were taken into consideration.

The timing of surgical intervention in IPN

The diagnosis of IPN has long been considered an indication for surgical intervention in patients with AP. With years of clinical practice by surgeons, the choice of timing of IPN surgical intervention has changed from the somewhat radical “early debridement” in the 1980s to the current “delayed surgery,” and the delayed intervention strategy has been widely recognized. Mowery et al^[2] analyzed 88 studies on AP, taking 3, 12 to 14, and 30 days after onset as time nodes, and found that patients in the delayed surgery group always had better outcomes at each

evaluation point, and in general, the patients who underwent surgery 30 days after the onset of disease had the best clinical outcomes. This is basically consistent with the view that the operation time should be 4 weeks after the onset of the disease, a result that has been published in many versions of guidelines in recent years.

The conditions of patients with AP are diverse and complex. In particular, some IPN patients will develop sepsis, multiple organ failure (MOF), or even die while waiting for delayed surgery. Moreover, some conditions, such as abdominal compartment syndrome (ACS), in the early stage of the disease cannot be solved via medical treatment and support interventions alone. Gao et al conducted a meta-analysis of 8 studies involving 742 patients and found that early invasive intervention did not increase mortality.^[3] For some patient groups, early intervention may also be necessary. Thus, whether all patients need to delay intervention for 4 weeks and can benefit from it has become an urgent problem to be solved.

IPN is a surgical infection occurring in the pancreas. In addition to antibiotics and supportive treatment, appropriate drainage is important for the treatment of the disease. Percutaneous catheter drainage (PCD) is considered an effective measure to control and treat IPN; it can improve the status of patients, reduce inflammatory mediators, and sources of local infection, and is an important way to delay debridement surgery. Approximately 30% of patients can recover after drainage treatment.^[4] It is generally believed that PCD should be performed for persistent pancreatic and peripancreatic infections or for symptoms caused by necrotic tissue and fluid pressing on the digestive and bile ducts. However, there is no consensus or standard on the timing of PCD, and a number of studies have shown that the duration period between PCD and the onset of disease can be as long as 9 to 75 days. The Dutch Pancreatitis Working Group administered a questionnaire survey to 87 pancreatic disease specialists worldwide, among whom 63 (72%) thought there was no need to set a clear time window for PCD, while the 24 who thought a time window needed to be set had an average time of 13 days.^[5] At present, some scholars still insist that PCD should be delayed, mainly based on the view that all forms of invasive intervention for IPN patients should be postponed until the necrosis is completely wrapped. In comparing surgery with PCD, they ignore the microaggressiveness of PCD and lack the support of high-quality research. In contrast, some retrospective studies have confirmed that early PCD has no adverse effects on or benefits for patients.^[6–8] The results of the POINTER experiment, which lasted more than 4 years, were announced in July 2021.^[9] In the treatment of IPN, there was no difference in outcomes between the primary end point, consisting of comprehensive complication index score (CCIs), and the secondary end point, consisting of death within 6 months, new multiple organ failure syndrome (MOFS), bleeding, gastrointestinal fistula, pancreatic fistula, incisional hernia and infection, internal and external secretory insufficiency, and grade III or higher complications. However, the number of intervention and drainage tubes was greater in the immediate drainage group than in the postponed drainage group. This randomized controlled study confirmed the advantages of delayed treatment, but the results

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were widely discussed as soon as they were published. In terms of the research protocol, some surgeons believe that the intervention time of the immediate intervention group was 24 days after the onset of disease; this was not early enough to be called “immediate” compared with the intervention time of 28 days after onset in the postponed group. In addition, endoscopic drainage was mixed with PCD, and specific treatment strategies for different parts of necrosis were also different. Confounding factors existed in the results. Previous studies by Rasslan et al^[10] and Mouli et al^[11] also indicate that some IPNs can be cured with antibiotics alone, and surgical intervention such as drainage might not be needed. The author’s perspective is that the inclusion criteria of POINTER research objects are fairly strict and patients’ basic physical condition is stable, which limits the interpretation of experimental findings. The final outcomes did not directly reflect the benefits of early drainage intervention for patients, but confirmed the safety of early intervention in the study’s limited population. According to recent studies, early drainage intervention with certain indications does not worsen the clinical prognosis.

Approximately 11% to 40% of AP patients have intra-abdominal hypertension (IAH) or ACS, which can deteriorate their general condition, inducing MOF.^[12] Early and appropriate relief of abdominal hypertension in severe AP (SAP) can improve patients’ prognosis. Drainage and surgery are vital ways to reduce intra-abdominal pressure. Singh et al^[13] reviewed 105 patients and found a significant rise in mortality from IAH in patients with acute peripancreatic effusion, and that early use of PCD was effective in mitigating IAH and reducing mortality.

According to current results, PCD can be used for drainage in a timely manner to relieve patients’ infection and poisoning status, as well as physiological status, after IPN is clearly diagnosed, without waiting for a specific operation time. For patients with IPN combined with ACS, abdominal drainage can be performed simultaneously to decompress and reduce inflammatory factors.^[12] The drainage tube should be removed to prevent intraperitoneal infection after the patient’s abdominal pressure drops and abdominal compliance improves. With the development of digestive endoscopy, endoscopic catheter drainage is also an effective drainage method for IPN. Trikudanathan et al^[14] reported that the use of endoscopic drainage in the early stage (within 2–4 weeks of onset) could improve the infection status of patients without increasing mortality. That said, endoscopic drainage has not been reported to reduce intra-abdominal pressure for IAH mitigation.

The main theoretical basis of delayed surgical operation is that patients in the early stage of the disease are still in a state of systemic inflammatory reaction and hardly bear the “blow” brought about by an invasive procedure. The necrotic material in the early stage of the disease is not fully liquefied and therefore limited, and it is difficult to completely remove it. Currently, most reports state that “4-week delayed surgery” was carried out based on traditional open surgery. However, in recent years, minimally invasive surgery technology represented by video-assisted debridement (VAD) has been gradually developed, which has less of an impact on the body than traditional open debridement. We focus on the clinical practice consensus of pancreatic necrosis released by the American Gastrointestinal Association in 2020, and the timing of surgical operation for patients with persistent infection and organ failure, has been adjusted from more than 4 weeks to more than 2 to 4 weeks.^[7] Contrary to the traditional view, van Grinsven et al^[15] explored the formation process of infectious pancreatic necrosis gas and walls in 2018, and found that walls had formed in most patients within the first 3 weeks after onset. In sum, the author asserts that when supportive therapy, antibiotics, and drainage fail to control infection, we should not blindly insist on postponing surgery. On the premise that patients can tolerate surgery in general conditions, VAD and other minimally invasive methods provide the technical circumstances

necessary for the implementation of early surgery. Early surgery may also be performed for pancreatic necrosis that has already formed localized wrapping within 4 weeks of onset. In sum, for the timing of IPN surgery, scientific surgical methods and accurate operational techniques provide more options for the window of treatment. The more methods there are, the more mature the techniques of doctors, and the less need to adhere to so-called fixed timing.

Surgical treatment strategies for IPN

The results of the PANTER study, published by the Dutch Pancreatitis Working Group in 2010, elevated “step-up” to a core position in surgical treatment strategies for IPN. The “step-up” strategy significantly reduced the incidence of the composite end point of severe organ failure and death compared to direct conventional open debridement.^[16] In addition, patients in the step-up group had a lower probability of incisional hernia and pancreatic endocrine and exocrine dysfunction during long-term follow-up.^[17] Hence, the “step-up” strategy has become the mainstream surgical treatment of IPN in the past 10 years.

Patients with IPN differ greatly from one another, and the composition and degree of liquefaction of pancreatic necrosis are different. When pancreatic necrosis is primarily solidified in patients receiving a step-up strategy, the effect of PCD is often unsatisfactory, and the relief of infection symptoms is not significant. Most of these patients require further pancreatic necrosectomy. In 2016, Hollemans et al^[18] published a study reporting that male sex, MOF, percentage of pancreatic necrosis, and heterogeneous collection were risk factors for failure of PCD drainage therapy, suggesting that it is difficult for such patients to delay necrosectomy by receiving PCD. In some patients, the lack of a safe and effective drainage channel will lead to treatment stagnation, or repeated drainage cannot completely remove necrotic tissue, resulting in a prolonged treatment period. Burek et al^[19] reported a case of sepsis and MOF after strictly following the “step-up” drainage strategy. It should be made clear that the original intention of IPN patients receiving PCD or endoscopic drainage is to reduce local necrosis and inflammatory mediators and to mitigate the effects of inflammatory symptoms. Some patients can be cured by drainage, and in most cases, drainage is used as a transitional treatment while waiting for delayed debridement. It is worth considering whether the “step-up” strategy and delayed operation are still necessary to treat patients who are in generally good conditions after supportive treatment when the necrosis is mostly solid and difficult to drain, or when the abdominal and retroperitoneal edema is serious and the anatomical relationship is chaotic, making a puncture impossible. Based on the above clinical experience, the author’s hospital began to perform “one-step” pancreatic necrosectomy in 2015; that is, VAD was performed directly for patients who did not receive PCD or endoscopic drainage when conditions were ripe. We conducted a retrospective cohort study on the “step-up” and “one-step” strategies. In the cohort, all the patients in the “one-step” group were IPN patients without PCD or endoscopic drainage who were directly treated with VAD, and the surgical methods primarily included the transomental bursa approach or the trans-retroperitoneal approach. The results showed that the “one-step” strategy could reduce the number of interventions and shorten the length of the patient’s hospital stay compared to the traditional “step-up” strategy. There was no difference in the incidence of new-onset organ function, postoperative hemorrhage, gastrointestinal fistula, and death or other short-term complications between the 2 treatment groups. There was no difference in the incidence of long-term complications such as pancreatic exocrine insufficiency, new-onset diabetes mellitus, or incisional hernia.^[20]

The successful implementation of the “one-step” strategy provides a new idea for the diversification of surgical strategies for IPN and indicates that for IPN, a complex and changeable

disease, the use of a personalized medical strategy for each patient is more feasible than the use of a uniform “model” treatment.

Surgical treatment approach for IPN

The history of pancreatic necrosectomy can be traced back to the end of the 19th century. After more than 100 years, this surgery has gradually formed into a blend of minimally invasive surgical debridement, open surgical debridement, and endoscopic debridement.

Open necrosectomy has the longest history and has been the only surgical method for IPN for quite a long time. The characteristics of this surgery, such as a large incision, heavy trauma, hemorrhage, and drainage cause serious damage to the body's tissue, and high mortality and complication rates are unavoidable facts. Most open necrosectomies were performed through the peritoneal cavity, which resulted in the spread of retroperitoneal infection to the peritoneal cavity. Such surgical procedures involving abdominal organs increase the risk of complications like intestinal fistula and intra-abdominal hemorrhage. As for the 3 types of surgical techniques, several studies have reported that the mortality of patients undergoing minimally invasive debridement or endoscopic debridement is lower than that of open necrosectomy.^[21] However, IPN patients' conditions are complex and diverse, and medical conditions in different regions are limited by technical conditions, so it is not feasible to cancel open necrosectomy and to implement minimally invasive surgery in a comprehensive way. If open necrosectomy is unavoidable, the surgeon should carefully screen the patient and control or downgrade the risk factors for complications and death. Husu et al^[22] found that old age, multiple underlying ailments, operation within 4 weeks, high white blood cell count, MOF, and the duration of organ failure were all factors contributing to death within 90 days in IPN patients undergoing open debridement. Other studies have reported that obesity is an independent risk factor for persistent organ failure and death in IPN patients.^[23] Henrik et al reviewed 109 patients who underwent open necrosectomy of necrotic tissue with an overall 90-day mortality of 22.9%, including 10.6% who underwent necrosectomy 4 weeks after onset. The study found a significantly higher risk of death when persistent organ failure was used as an indication for the surgery.^[22] In 2019, the Dutch Pancreatitis Working Group published a multicenter study involving 639 cases of necrotizing pancreatitis. Persistent organ failure in the early stage of ANP did not increase mortality, and mortality was not associated with the duration of organ failure.^[24] Hence, if open necrosectomy is to be performed, the surgical indications should be accurately grasped, and debridement due to MOFS should not be performed in the early stage of the disease.

With the development of surgical instruments and techniques, minimally invasive methods represented by laparoscopy and endoscopy play an important role in pancreatic surgery. The results of the PANTER study further established the value of minimally invasive debridement techniques in the “step-up” strategy in IPN treatment. Currently, commonly used surgical methods for minimally invasive pancreatic necrosis tissue removal include small incision debridement (with or without video assistance), total laparoscopic pancreatic necrosectomy, and laparoscopic-assisted pancreatic necrosectomy. Compared to open surgery, these techniques cause less tissue damage and less trauma. Laparoscopic debridement of IPNs has advantages such as a lower incidence of complications and reduced blood loss.^[25] Compared to traditional open surgery, the retroperitoneal approach of minimally invasive necrosectomy leads to lower rates of postoperative organ failure and a shorter time spent in the intensive care unit (ICU), but a higher frequency of operation.^[26] In the author's opinion, total laparoscopic surgery has more advantages in debridement of the necrotic material closer to the posterior gastric wall, and continuous drainage can be achieved by anastomosis of the abscess cavity to the gastric wall

after debridement through the posterior gastric wall. However, for most IPN patients, the author preferred VARD because the infectious lesions were mainly located in the retroperitoneum and VARD did not enter the abdominal cavity. Laparoscopically assisted microincision debridement can be performed by either disforming the sinus of existing drainage tubes or by opening a new channel directly to the area where necrosis accumulates. This procedure on the one hand can alleviate damage and on the other can reduce the risk of the spread of infectious necrotic material into the abdominal cavity. In 2016, our center reported the “step-up” IPN treatment strategy based on minimally invasive means. Among the 54 patients, 59.26% (32/54) received minimally invasive small incision debridement and VARD debridement; the total mortality of the group was 7.4%, and no patient received open surgery.^[27] Laparoscopic transgastric necrosectomy (LTGN) was used to treat wall-off necrosis (WON) cases with sinistral portal hypertension, and it is confirmed to be a safe and effective way to deal with WON compared to laparoscopic-assisted trans-lesser sac necrosectomy.^[28] According to the specific conditions of pancreatic necrosis and the systemic status of patients, the selection of appropriate minimally invasive methods and surgical approaches can safely and effectively treat IPN.

The application of endoscopy in the treatment of IPN began in the 1990s. In recent years, due to the development of endoscopic instruments and updates to endoscopic technology, an increasing number of studies have begun to report endoscopic necrosectomy. Especially after 2010, a large number of studies have been carried out on the “step-up” strategy via endoscopic methods. In contrast to the “delay” principle of surgical intervention, Trikudanathan et al^[14] found in 2018 that for patients with IPN complicated by organ failure, endoscopic “step-up” debridement was more likely to be performed within 4 weeks of onset; the organ function of such patients improved after treatment, and the complication rates and mortality did not increase.^[14] In addition to the timing of surgery, other features of endoscopic surgery compared with surgical debridement have also drawn much attention. Pancreatitis Endoscopic Transgastric vs Primary Necrosectomy in Patients with Infected Pancreatic Necrosis (PENGUIN) trial reported that endoscopic necrosectomy could reduce the proinflammatory response as well as the composite clinical end point compared with surgical necrosectomy.^[29] Minimally Invasive Surgery vs Endoscopy Randomized (MISER) trial was a randomized controlled trial (RCT) comparing minimally invasive endoscopic and surgical “step-up” strategies; the results showed no significant difference in mortality or new-onset organ failure between the 2 groups. The incidence of gastrointestinal fistula and pancreatic fistula was lower in the endoscopic group (0 vs 28.1%, $P = .001$), and the average number of major complications caused by “new MOFS, new systemic disorders, intestinal or pancreatic skin fistula, internal organ bleeding and perforation, and death within 6 months of follow-up” was lower in the endoscopic group ($[0.15 \pm 0.44]$ vs $[0.69 \pm 1.03]$; $P = .007$).^[30] “TENSION,” another RCT study, also reported no significant difference in mortality and complication rates between the 2 groups, but a lower incidence of pancreatic fistula and a shorter hospital stay in the endoscopic “step-up” group.^[31] At long-term follow-up, pancreatic insufficiency and quality of life did not differ between groups.^[32] Endoscopic cystogastrostomy creates a smaller fistula than surgical cystogastrostomy and the fistula closure is faster.^[33] These studies have confirmed the effectiveness and safety of endoscopic strategies in the treatment of IPN. However, since endoscopic technology is limited by the anatomical structure of the digestive tract and endoscopic surgery is constrained by the instruments available, operating space, and range of motion, the endoscopic “step-up” strategy is generally considered to have better efficacy in the treatment of necrosis near the posterior wall of the stomach. That said, endoscopic debridement has limitations for necrotic tissues at

certain sites, such as the retrocolonic space and the pelvic cavity.^[34] It should be noted that endoscopic treatment requires a professional team with extensive experience in digestive endoscopic treatment. The author believes that patients with poor efficacy or complications after endoscopic treatment can still receive minimally invasive surgical intervention, and the author has reported 17 cases with promising results.

Limitations

As a narrative review, no data was re-analyzed in this article. The collection and description of literature is still inevitably subjective. Moreover, this article only conducts a literature review based on the current mainstream views and international consensus on the treatment of IPN, and does not specifically describe other theories and studies presented in the process of forming these consensuses.

Conclusions and future perspectives

In the context of multidisciplinary diagnosis and treatment, IPN treatment is improving daily, and multiple RCT studies have provided more evidence for us to develop new treatment strategies and methods. At present, however, there are still a number of unresolved questions related to treatment for IPN. The role of early PCD remains to be explored. In the era of minimally invasive surgery, small incision minimally invasive debridement or laparoscopic necrosectomy has been in a leading position in the surgical treatment of IPN. The “step-up” strategy has been used as the mainstream idea to influence the treatment of IPN for nearly 10 years. However, studies on the “one-step” strategy and “skip-up,” “step-jump,” “step-across” and other strategies by different teams in China have confirmed that some patients will benefit from direct surgical treatment. Endoscopic therapy, as a “rising star” in IPN treatment, has advantages in reducing postoperative complications. Notwithstanding, it still has limitations in its indications compared to minimally invasive surgery. At present, IPN treatment involves multiple disciplines such as intensive critical care, pancreatic surgery, endoscopy, and interventional therapy departments, and patients will benefit from MDT mode treatments in high-value centers with rich experience. The success of IPN treatment depends on well-developed medical facilities and experienced and professional team. The treatment of IPN must be personalized. Appropriate surgical timing and strategies should be considered according to patients’ conditions, and the treatment of all patients should not be fixed in the same mode.

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Author contributions

FC and WM collected the data, designed and wrote the manuscript. FL initiated, revised, and finalized the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

Not applicable.

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