

From “step-up” to “step-jump”: a leap-forward intervention for infected necrotizing pancreatitis

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Acute pancreatitis (AP) can vary widely in its severity, from being clinically self-limiting to a rapidly fatal course.^[1] Necrotizing pancreatitis (NP) is the most serious form and is associated with a poor prognosis; the mortality rate is approximately 15%, or up to 30% for cases of infected necrotizing pancreatitis (INP), which often progresses to sepsis and multiple organ failure, the major cause of death and severe complications.^[2] The approach to the management of INP has significantly changed during the last 20 years and continues to evolve with the accumulation of experience, new techniques, and research data. Major surgical intervention and debridement were once the mainstay of therapy for patients with symptomatic necrotic foci, but a minimally invasive approach that focuses on percutaneous and/or endoscopic drainage or debridement is now favored.^[2] The “step-up” approach, which involves minimally invasive techniques, represents a new paradigm for the treatment of patients with INP, and open pancreatic debridement is now considered to be the final step in the treatment of NP.^[2]

The landmark Dutch multicenter randomized minimally invasive step-up approach *vs.* maximal necrosectomy in patients with acute necrotizing pancreatitis (PANTER) trial showed that step-up therapy ranging from percutaneous catheter-mediated drainage to minimally invasive surgery, which comprised video-assisted retroperitoneal debridement, was as effective as open surgery and was associated with lower incidences of complications including organ failure, incisional hernia, diabetes, and others.^[3] Recently published long-term follow-up data from the PANTER trial have further established the superiority of the minimally invasive step-up approach. Specifically, there was no difference in the need for re-intervention between the step-up and open necrosectomy arms over an 86-month period.^[4] In addition, participants in the step-up

arm had lower incidences of incisional hernia, pancreatic exocrine insufficiency, and diabetes.^[4]

The PANTER trial has received widespread attention and has led to the minimally invasive treatment-based step-up strategy becoming the gold-standard method for the treatment of INP.^[2] Nevertheless, some limitations of this study that could have affected the final outcomes should be highlighted. (1) The participants in the study were not stratified according to the characteristics of the necrotic tissue. In general, completely liquefied necrotic tissue should be classified as “wet” necrosis, for which drainage is the primary treatment strategy. In contrast, solid or semi-solid necrotic tissue should be classified as “dry” necrosis, for which debridement is the optimal intervention strategy. The results showed that of the patients assigned to the step-up approach, 35% were successfully treated using ultrasonographically or computed tomography-guided percutaneous catheter drainage (PCD) only, which suggests that the pancreatic necrosis of some of the participants was dominated by “wet” necrosis. However, a considerable proportion of the participants with “wet” necrosis were in the control group and underwent direct laparotomy, which goes against the quoted treatment principles. Therefore, we believe that a comparison of step-up *vs.* up-front open surgery is probably not methodologically appropriate. The first-choice treatment for a single retrogastric or retroperitoneal left-sided focus of necrosis would be step-up, and up-front surgery could be regarded as over-treatment for such cases. (2) It is well known that the amount of surgery a surgeon performs is closely related to the quality of their surgery. However, in the PANTER trial, the amount of pancreatic surgery, and especially open pancreatic necrosectomy, undertaken by the surgeons who performed open debridement procedure was not stated. (3) Notably, no difference between the groups was identified with respect to mortality in the study sample as a whole. (4) The sample size was relatively small; therefore, further larger,

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multicenter clinical trials are required to validate the findings.

The specific situation differs for each patient; therefore, individualized treatment should be adopted for patients with NP. Burek *et al*^[5] reported the case of a patient who was treated in strict accordance with the step-up strategy and eventually died of severe sepsis, and the authors correctly state that, in some cases, aggressive, open surgical treatment is more effective and that a delay in surgery can result in deterioration of the patient and the development of severe sepsis. A study by Harfouche *et al*^[6] showed that patients who experience a failure of drainage during the management of NP are at high risk of morbidity and mortality and fare worse overall than patients who undergo surgery as the primary intervention. In this study, patients with NP and a high Acute Physiology and Chronic Health Enquiry II score might have benefitted from surgical intervention, rather than a drainage-first approach. Another retrospective study showed that patients who undergo a minimally invasive procedure before surgical debridement are more acutely ill, and when they are “stepped-up” to open pancreatic debridement they experience significantly greater post-operative morbidity.^[7] Taken together, these findings suggest that there can be negative consequences to a one-size-fits-all approach to the management of severe AP, with or without necrotizing and/or infected components. Thus, the real-world clinical scenario may be that surgery may be performed late.

Some patients may benefit from a step-up intervention strategy but one size does not fit all. INP can present with a range of clinical and morphological features, and therefore not all patients are likely to benefit from the same approach to management. The incomplete debridement that characterizes minimally invasive techniques necessitates a larger number of procedures than is necessary if open necrosectomy is performed.^[8] Thus, an overemphasis on the use of step-up can cause the optimal timing of surgical treatment to be missed, which may lead to irreversible sepsis. In contrast, surgical necrosectomy permits thorough debridement during a single procedure, which may be advantageous, especially in cases of widespread necrosis. Therefore, in selected cases, a “step-jump,” surgery-first approach should be taken, without the necessity to perform PCD or endoscopic intervention as the first step-up therapy. Moreover, in patients who fail to improve or suffer complications after the minimally invasive management of necrosis, open necrosectomy provides a bailout treatment option.

In the early stages of the onset of AP, it is extremely difficult to distinguish necrotic tissue from normal tissue. Therefore, early surgery, involving large incisions and wide debridement, can cause damage to normal pancreatic tissue, blood vessels, and other organs, which may lead to massive fatal hemorrhage, intestinal fistula, or other catastrophic complications. As a result, delayed and minimally invasive interventions have become the expert consensus approach during the past two decades.^[2] Minimally invasive strategies may represent definitive treatments in some patients. However, it is unclear whether minimally invasive techniques are superior to open necrosectomy. Indeed, in experienced hands, open pancre-

atic necrosectomy remains a safe and effective technique. In a subsequent series of 167 patients that were treated at the Massachusetts General Hospital, the mortality rate was 20.3% in those who underwent open debridement and closed packing during the first 28 days following the onset of symptoms but only 5.1% when debridement and closed packing was performed after 28 days.^[9] Cao *et al*^[10] developed a one-step laparoscopy-assisted approach to the treatment of INP, in which percutaneous drainage was omitted and direct laparoscopy-assisted necrosectomy was performed. The findings suggested that the one-step approach is safe, is not associated with higher incidences of complications or mortality, and is associated with fewer procedures and a shorter total hospital stay than the step-up approach. Recently, a multicenter study conducted in Japan showed no significant differences in mortality between patients who underwent secondary open necrosectomy for INP compared with those who underwent minimally invasive treatment.^[11] The tendency to declare every minimally invasive approach as “superior,” simply because it is less invasive, needs to be tempered by the reality that open surgery is a very safe and effective treatment modality when performed in centers that undertake a large amount of pancreatic surgery.

It is important to note that the high mortality rate of participants in the open necrosectomy group can be explained by the larger numbers of patients in this group who were in a poor condition and/or had severe underlying pancreatitis and extensive retroperitoneal necrosis. A retrospective study conducted in Finland showed that the indications for open necrosectomy are associated with mortality and that the risk of mortality is higher if patients are deteriorating or do not show clinical improvement in their organ failure before open necrosectomy.^[12] Furthermore, open necrosectomy can be performed without a high risk of mortality if multiple risk factors for surgery are absent.^[12] In this study, surgical necrosectomy was performed either in cases where step-up was not feasible or where rescue was required following endoscopic or radiologic failure. This means that the patients who underwent open surgery were often critically ill and/or refractory to less invasive measures, and therefore, represented the most challenging cases of NP. In this context, the indications to perform surgery, rather than the surgical procedure itself, should be considered as a poor prognostic factor. We believe that a direct comparison of step-up and up-front open surgery is probably not methodologically appropriate because each is typically performed in different groups of patients, with the latter approach being associated with a poorer prognosis because of the presence of multiple and non-communicating walled-off necrotic foci, or more severe illness, which render the step-up approach unfeasible. Therefore, further studies are needed to clarify the roles of up-front and rescue surgery in the modern era.

It must be acknowledged that some patients with NP who are refractory to minimally invasive therapies may benefit from primary surgical debridement. Thus, a critical, unanswered question is which patients would benefit from surgical debridement as the first-line approach. Unfortunately, to answer this question using a prospective

trial would be immensely challenging and likely impossible because relatively few patients with NP are treated by most centers, and because of the heterogeneity of the volume of necrosis, its anatomic distribution, and the general physiologic condition of the patients. Consequently, little evidence has been presented to date regarding which patients would benefit from surgery or require open pancreatic debridement. Further studies into the characteristics of patients that portend the failure of percutaneous drainage, as well as the factors that contribute to poor outcomes in such patients, are needed to guide clinicians as to when to adopt a more aggressive, open approach to the management of INP. Thus, the ultimate goal of any evaluation strategy should be to discern which patients would benefit from direct surgical intervention.

In recent years, minimally invasive interventions have become the first-choice option, and the step-up approach is considered to be the gold-standard treatment for INP. However, the complexity and variability of this disease necessitate a targeted approach that depends on the patient's specific circumstances. There is no doubt that surgical pancreatic debridement can be performed safely and remains an important management strategy for properly selected patients. Patients who are destined to require surgical intervention should be offered a step-jump treatment strategy in place of the conventional step-up sequence of therapeutic procedures. In the future, we need to distinguish different situations of patients and construct clinical prediction models for the various interventions for INP, which would permit patients to be more appropriately treated.

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Conflicts of interest

None.

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