



Interventional strategies in infected necrotizing pancreatitis: Indications, timing, and outcomes

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Abstract

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases and remains a life-threatening condition. Although AP resolves to *restitutio ad integrum* in approximately 80% of patients, it can progress to necrotizing pancreatitis (NP). NP is associated with superinfection in a third of patients, leading to an increase in mortality rate of up to 40%. Accurate and early diagnosis of NP and associated complications, as well as state-of-the-art therapy are essential to improve patient prognoses. The emerging role of endoscopy and recent trials on multidisciplinary management of NP established the "step-up approach". This approach starts with endoscopic interventions and can be escalated to other interventional and ultimately surgical procedures if required. Studies showed that this approach decreases the incidence of new multiple-organ failure as well as the risk of interventional complications. However, the optimal interventional sequence and timing of interventional procedures remain controversial. This review aims to summarize the indications, timing, and treatment outcomes for infected NP and to provide guidance on multidisciplinary decision-making.

Key Words: Pancreatitis; Acute necrotizing pancreatitis; Necrosis; Superinfection; Endoscopy; Surgery

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Core Tip: Acute pancreatitis remains a potentially life-threatening disease. Necrotizing pancreatitis (NP) is associated with superinfection and increases the mortality rate. We summarized the current evidence and clinical recommendations of multidisciplinary approaches focusing on conservative, interventional, and surgical treatment. The interventional approach is often required as a first step in treating infected NP, while further options include minimal invasive or an escalation to open surgical treatment. Although this “step-up approach” is well-established, the exact timing, sequence, and procedure choice remain controversial; this review aims to summarize current evidence and to provide guidance for decision making in clinical practice.

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INTRODUCTION

Acute pancreatitis (AP) is one of the most common and severe gastrointestinal diseases[1]. The rate of AP-related hospitalization in the United States increased from 65.38 to 81.88 per 100000 United States adults per year from 2001 to 2014[2].

The pathophysiology of AP is characterized by acinar cell injury leading to premature intrapancreatic activation of digestive proteases. ATP depletion and mixed lineage kinase domain-like protein phosphorylation lead to acinar cell necroptosis and necrosis[3]. This results in a cascade effect leading to autodigestion of the pancreatic parenchyma. The acinar cell injury and autodigestion can be induced by different mechanisms; recent publications discuss, for example, the role of hypercalcemia and organelle dysfunction. Cholecystokinin, biliary acids, and alcohol consumption can lead to increased Ca^{2+} efflux by the endoplasmic reticulum (ER). In turn, hypercalcemia can damage the mitochondrial membrane, reducing ATP production and hence the function of the Ca^{2+} efflux mechanisms of the cell itself, which increases the intracellular Ca^{2+} levels even further. This intracellular Ca^{2+} overload ultimately leads to the release and activation of digestive enzymes, which results in premature activation of trypsin. In addition, bile acids, alcohol, and other pancreatic toxic substances can trigger the acinar cells themselves, leading to higher secretion of trypsin[4-6].

AP can be classified as either interstitial edematous or necrotizing pancreatitis (NP). While inflammation and edema of the pancreatic parenchyma and peripancreatic tissues characterize intestinal edematous pancreatitis, further pancreatic or peripancreatic necrosis is known as NP[6], which is a potentially life-threatening disease associated with a 15% mortality rate. In approximately a third of patients with NP, superinfection (fungal or bacterial infection) of necrosis occurs during the clinical course, mostly within 2 to 4 wk after disease onset. Infected NP (INP) results in an even higher mortality rate of up to 30% to 39% (Figure 1)[7-9]. The major causes of INP are obstructing gallstones (up to 50%) and alcohol abuse (20%)[10].

Several scores were introduced in order to predict the severity of AP and its mortality. A retrospective study from 2013 comparing some of these scores revealed that especially the Bedside Index for Severity in Acute Pancreatitis (BISAP) and Acute Physiology and Chronic Health Evaluation (APACHE-II) score stand out compared to scores like the computed tomography (CT) severity index, Ranson Score, body mass index, or hematocrit in terms of predicting severity, organ failure, and death. The BISAP score is a combination of the following five parameters, each worth one point: Altered mental state, blood urea nitrogen > 25.2 mg/dL or more, positive systemic inflammatory response syndrome criteria, age over 60 years, and pleural effusion on CT scan. In comparison, the APACHE-II score uses 14 different parameters, ranging from age to the Glasgow Coma Scale[11].

Another applicable score in INP is the Marshall Score, which determines the presence of organ failure, which, according to the 2012 revised Atlanta Classification of AP, is a criterion that differentiates between mild (no organ failure), moderate (organ failure after less than 48 h), and severe (organ failure after more than 48 h) pancreatitis. The Marshall Score assesses the respiratory system on a scale from 0 to 4 using $\text{PaO}_2/\text{FIO}_2$, the renal system using serum creatinine in mg/dL, and the cardiovascular system using the systolic blood pressure in mmHg. A score of 2 or higher for any of the systems indicates organ failure[12].

The clinical management of INP is complex and involves a multidisciplinary team of intensive care specialists, gastroenterologists, and surgeons. Recent trials have provided important insight into the disease mechanisms and have optimized the treatment strategies. However, the indications, timing, and outcomes of different interventional strategies remain controversial.

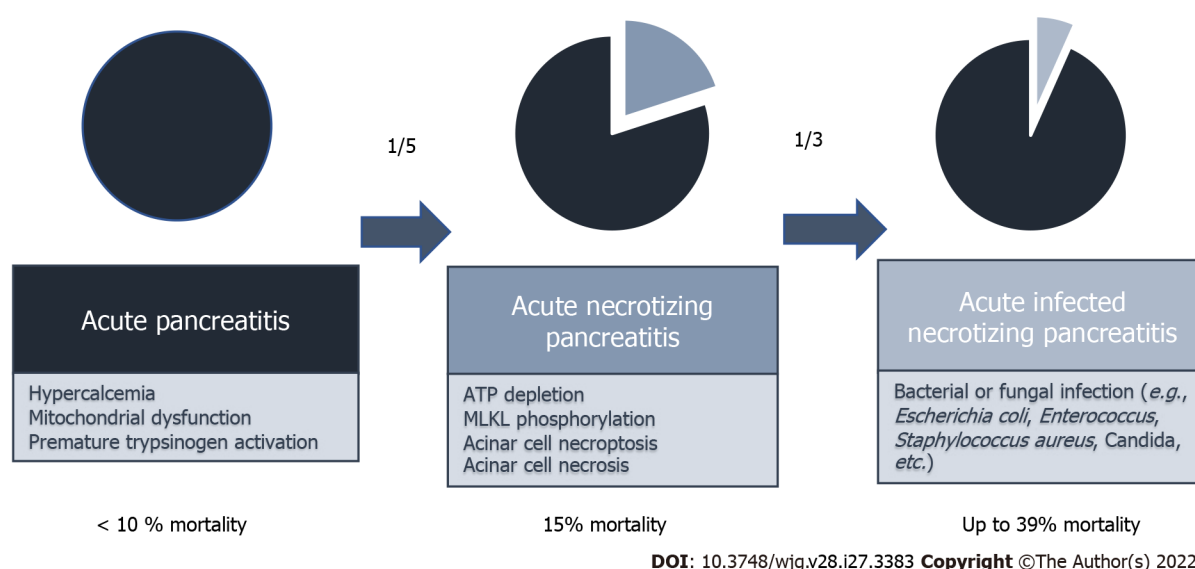


Figure 1 Mortality rates of acute pancreatitis and pathomechanisms. The mortality rate of all patients with acute pancreatitis (AP) is less than 10%. One-fifth of the patients developed necrotizing AP by ATP depletion, MLKL phosphorylation, acinar cell necroptosis, and/or acinar cell necrosis. One-third of the patients with necrotizing AP developed bacterial or fungal infection. The mortality rate of the infected necrotizing pancreatitis is up to 39%.

PHASES OF AP

According to the 2012 revised Atlanta classification of pancreatitis, two AP phases can be differentiated: the early (< 1 wk after onset) and late (> 1 wk after onset) phases. The early phase is characterized by the first clinical signs of pancreatitis: Abdominal pain, biochemical findings, and imaging findings consistent with pancreatitis. During this time, a pro-inflammatory sterile response occurs, which can lead to systemic inflammatory response syndrome (SIRS)[13]. Nevertheless, AP is self-limited in more than 80% of patients, and treatment in the early phase consists of supportive care instead of a curative intervention[14]. However, necrosis and acute necrotic collection (ANC) can occur in the late phase. ANC is considered a local complication of AP and is characterized by a collection of both fluid and necrosis without a defined wall[8]. ANC can resolve spontaneously or eventually become encapsulating, which allows the collection to become more organized within a well-defined inflammatory wall [15,16]. This process takes approximately 4-6 wk and the end-product is called a walled-off necrosis (WON)[17]. Once WON is diagnosed, whether the pancreatic or peripancreatic necrotic tissue and ANCs are sterile or infected must be determined to plan the subsequent treatment course. Superinfection of acute NP increases the mortality rate (24% *vs* 3.5%)[18,19]. In order to prevent SIRS, sepsis, and multiple (respiratory, cardiovascular, hepatic, and renal) organ failure, the treatment goal is to remove the infected non-vital tissue[13,18,20].

DIAGNOSIS OF ACUTE INP

The diagnosis of AP is mostly based on clinical symptoms; the major ones being abdominal pain, fever, nausea, and vomiting. The diagnosis is further narrowed by measuring the levels of serum amylase and/or lipase. As a diagnostic criterion for pancreatitis, these markers exceed the physiological range by approximately three times. Characteristic imaging findings, such as enlargement of the pancreas and hypodense areas within the parenchyma and/or the peripancreatic tissue, are radiological imaging criteria[8,17,21].

The primary imaging modality within the first 48 h is a transabdominal ultrasound, primarily to determine the need for cholecystectomy for biliary pancreatitis. If the diagnosis of AP remains uncertain, a CT scan can be performed. However, changes on CT are most evident approximately 72 h after AP onset[21].

To diagnose NP, contrast-enhanced CT (CECT) is the preferred imaging modality, as it can identify the presence of gas in the necrotic collection. Magnetic resonance imaging can also be used but is less sensitive than CECT[22]. The diagnosis of infected necrosis is based on clinical criteria including fever and rising serum inflammatory markers[23].

INP REQUIRES A MULTIDISCIPLINARY APPROACH

INP requires both closely monitored intensive care and interventional approaches to remove infected necrotic areas. Endoscopic interventional options involve endoscopic drainage and/or endoscopic necrosectomy. Further interventions are percutaneous transgastric drainage, minimally invasive or open necrosectomy. Using the acronym “PANCREAS”, Gomes *et al*[24] summarized eight important steps in the management of severe AP: Perfusion, analgesia, nutrition, clinical and radiological assessment, endoscopy, antibiotics, and surgery.

Historically, INP patients have undergone early open debridement of necrotic tissue (median timing of the operation 21[25] to 28[26] d), mostly followed by local continuous lavage[26]. Recently, interventional strategies have shifted towards a so-called “step-up approach,” which involves endoscopic or surgical interventions that comprise open and minimally invasive procedures. The approach starts with simple, less invasive interventions like endoscopic drainage, and escalates to more invasive and finally surgical procedures if these approaches fail.

CONSERVATIVE TREATMENT

INP patients require close monitoring and may need to be admitted to intensive care treatment due to the risk of sepsis and consequent organ failure[27]. The major components of conservative therapy are fluid administration, nutrition, and antibiotics.

FLUID ADMINISTRATION

Hypovolemia is a constant risk in AP patients; moreover, installing fluid infusions and closely monitoring patient circulation parameters is therefore essential. The duration of intravenous infusions as well as the total volume of fluids per day, are subject to ongoing debate[24].

A recent meta-analysis analyzed the impact of early aggressive fluid therapy (infusion rate of 3-5 mL/kg/h in the first 24 h) as compared to non-aggressive hydration. Eleven trials were included, and the authors could not detect a difference in mortality rate; however, aggressive fluid therapy increased the risk of acute kidney injury and pulmonary edema. Furthermore, there was no difference in overall outcomes such as incidence of SIRS, organ failure, or pancreatic necrosis for both therapeutic strategies [28]. Another study demonstrated that early rapid fluid therapy is associated with persistent organ failure, primarily of the respiratory system[29].

Recent studies have favored Ringer’s lactate solution as the fluid of choice as opposed to saline solution, as the former reduced systemic inflammation[30]. Recent studies have concluded that the optimal AP regimen involves 3-4 L of Ringer’s lactate solution every 24 h and predefined checkpoints at 6-8 h in order to tailor the fluid management to the condition of the patient. Furthermore, measuring urine output, intraabdominal pressure, and vital signs can help adjust the regimen of fluid therapy[31].

NUTRITION

While fasting was considered helpful in AP in the past, current evidence supports early oral or enteral nutrition even if patients experience AP-related complications. As patients with acute NP have increased energy requirements and sustained protein catabolism, an early start of enteral nutrition within the first 48 h of symptom onset is the current standard of care[32]. Regarding nutrition protocol, 25 kcal/kg/d up to a maximum of 30 kcal/kg/d with 1.2-1.5 g/kg of protein per day is recommended [24]. As compared to parenteral nutrition, enteral nutrition is associated with a lower rate of infectious complications and organ failure, shorter hospital stay, and reduced mortality rate[33,34].

ANTIBIOTICS AND PANCREATIC FUNGAL INFECTION

In contrast to patients with general AP, INP patients require immediate antibiotic therapy starting as soon as the diagnosis of INP is confirmed. INP should be initially treated with empirical antibiotics covering both aerobic and anaerobic Gram-negative and Gram-positive microorganisms, such as Imipenem or Ciprofloxacin[35]. A CT-guided fine-needle aspiration (FNA) can help design a more targeted treatment plan. The bacteria most frequently identified in IPN are *Escherichia coli*, *Enterococcus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Pseudomonas spp.*, and *Streptococcus spp.*[36].

Although antibiotic therapy is an essential tool in the treatment of INP patients, there is insufficient evidence to support the role of antibiotic prophylaxis after the diagnosis of sterile pancreatitis in order to prevent superinfection[36-38].

The use of prophylactic antibacterial therapy and duration of antibacterial therapy have been observed to increase the incidence of pancreatic fungal infection, which is a condition in patients with NP that is associated with increased mortality, intensive care unit admission rate, and length of stay. Its incidence was 26.6% in a study including 2151 patients with NP[39].

INVASIVE TREATMENT

Treatment planning and determining therapy concepts in INP patients should be performed within a multidisciplinary team of surgeons, interventional radiologists, and gastrointestinal endoscopists at experienced centers. Specialists should assess the feasibility of different access routes (transgastric, transduodenal, percutaneous, retroperitoneal, laparoscopic, or laparotomic) and weigh the treatment options, while considering the individual clinical condition of each patient (Table 1).

ENDOSCOPY

Endoscopy plays an emerging role in the treatment of INP[40]. Interventional approaches such as the placement of plastic or metal stents for endoscopic transluminal drainage (ETD) or direct necrosectomy are endoscopically feasible[41].

ETD AND STENT CHOICE

ETD is performed as the standard first step of endoscopic INP treatment. The aim of this procedure is to establish a temporary connection between the gastric cavity and necrotic cavity in the adjacent pancreas in order to drain necrotic collections.

ETD is performed with the assistance of endoscopic ultrasound, which helps avoid puncturing of vessels (*via* color doppler) or targets other than the necrotic collections[42]. The endoscopist then places either a plastic, double pigtail stent; a self-expandable metal stent (SEMS); or a lumen-apposing metal stent (LAMS). The metal stents are larger in diameter (15-20 mm) than the plastic stents (2.33-3.33 mm) and provide access for potential subsequent debridement (Figure 2). SEMS are not commonly used, as they have been reported to migrate into the collapsed fluid collection, posing a risk of major bleeding [43]. LAMS are designed to prevent migration and minimize the risk of leakage with their apposing features[44,45]. Another advantage of LAMS over plastic stents is the delivery system *via* a single-step platform, resulting in a shorter intervention time[46]. Retrospective studies comparing drainage with either LAMS or plastic stents found that the procedure time is significantly shorter for LAMS drainage [47,48]. One of these studies also shows that LAMS drainage results in increased clinical success, reduced need for surgery, and a lower recurrence rate[47].

A more recent randomized clinical trial, however, compared both stent types in a total of 60 patients (31 undergoing LAMS placement and 29 undergoing plastic stent placement) and found that LAMS was not superior to plastic stents. The authors detected no difference in treatment success, the number of procedures required, length of stay, adverse events (within < 3 wk of LAMS removal), readmissions, or overall treatment costs[49,50]. Moreover, the study showed significant stent-related adverse events if LAMS were left in place for more than 3 wk. Given these heterogeneous results, future studies are needed to further evaluate the outcomes of different ETD strategies. Nevertheless, the treating medical team should consider the different procedure duration, since the average time to place the LAMS is shorter compared to plastic stents (15 *vs* 40 min, $P < 0.001$)[51].

ENDOSCOPIC NECROSECTOMY

If the clinical condition of INP patients fails to improve 72 h after ETD, necrosectomy should be considered. Endoscopic transluminal necrosectomy (ETN) can be performed, using a LAMS as access route to the necrotic cavity. With help of forceps, nets, and lavage techniques with saline or hydrogen peroxide, the necrotic tissues are removed endoscopically. ETN can be performed several times if necroses cannot be removed in one procedure[52,53]. It is important to consider that multiple ETN attempts also cause an increased risk of procedure-related complications such as bleeding or perforation [42].

Table 1 Overview of possible interventions in infected necrotizing pancreatitis

		Indications	Contraindications	Most common complications	Ref.
Interventions	Endoscopic transluminal drainage	Standard first step for INP, standard for PFC treatment	Unencapsulated collections, distance from gastroduodenal duct (> 1 cm), vascular pseudoaneurysms	Major bleedings, perforation, post-procedure infection, recurrence, migration of the stent	[37, 38, 40]
	Endoscopic necrosectomy	No improvement in clinical condition within < 72 h after ETD, follow-up treatment	Large necrotic areas, dense necrosis, disconnected duct	Bleeding, perforation, pancreatic fistula, infections	[37, 48, 50]
	Percutaneous catheter drainage	Hardly accessible ANC, ETD not feasible, as combination with ETD	Intracystic haemorrhagia, pancreatic ascites	Intestinal fistula, infection	[36, 51]
	Open surgery	Infected necrosis, suspected perforation, abdominal compartment syndrome, ischemia, intrabdominal haemorrhagia, poorly walled off necrosis, final treatment option if other interventions fail	No clear contraindications reported	Bleeding, infection, perforation, multi-organ failure	[52, 53]
	Minimally invasive surgery	Infected necrosis	Extensive or hardly accessible collections	Bleeding, infection, perforation	[44, 57, 58]

INP: Infected necrotizing pancreatitis; ANC: Acute necrotic collection; ETD: Endoscopic transluminal drainage.

If a transgastric access is not possible or WONs are located in an inaccessible lateral position, a sinus tract endoscopy (STE) may be an option. In order to perform STE, a CT-guided percutaneous drainage catheter is placed 10 d prior to the procedure. The catheter causes the tract wall to mature, so the insertion of an adult gastroscope under fluoroscopic control can be performed safely. The necrotic cavity is lavaged and necrotic tissue is removed, as is done in the ETN procedure (Figure 3)[54].

Endoscopic necrosectomy reduces the rate of surgical interventions[55]. However, these interventions are limited to small necrotic areas and can be very time consuming (60-120 min)[56].

PERCUTANEOUS CATHETER DRAINAGE

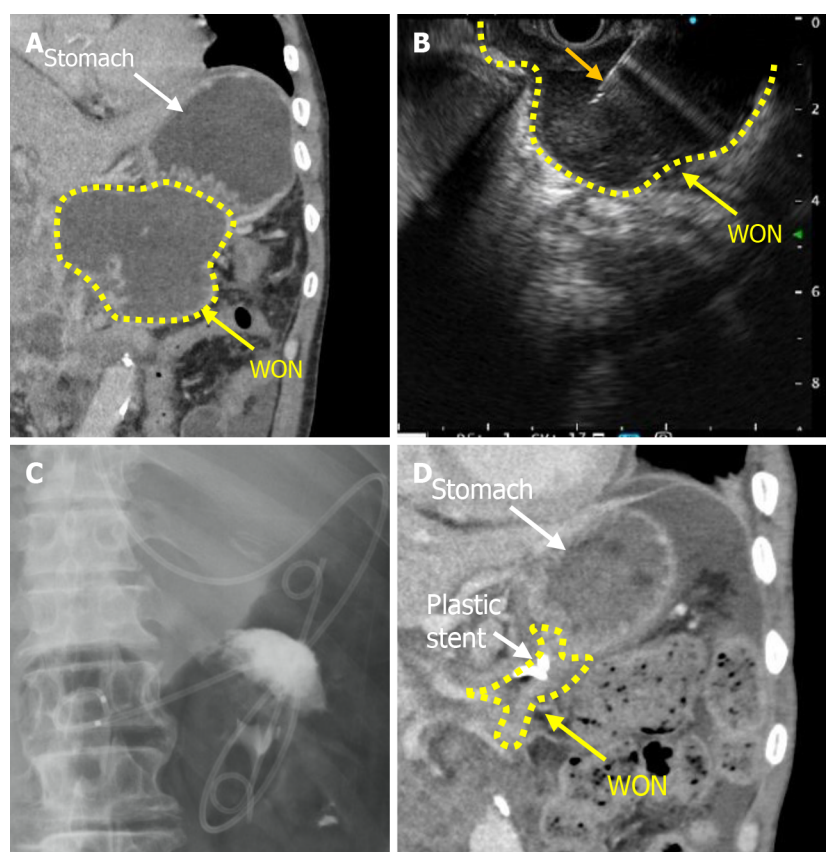
Percutaneous catheter drainage (PCD) is often used prior to endoscopic necrosectomy if the ANC is located in the flank or pelvic region and access *via* ETD is not possible. An interventional radiologist places a general-purpose pigtail drainage catheter into the necrotic collection using the Seldinger technique *via* the most direct transperitoneal route. The preferred route for PCD is through the retroperitoneum. In this case, the drain can be used to guide potential further minimally invasive retroperitoneal necrosectomy (*i.e.*, video-assisted retroperitoneal debridement or STE). A combination of endoscopic transluminal and PCD (also known as dual-modality drainage) is a further option in patients with large collections extending into the paracolic gutters or pelvic region[57]. PCD is the least invasive intervention and was the only intervention needed for patients with INP in 35% (15 out of 43) patients in the randomized PANTER trial[40].

SURGERY

Larger, more complex, and endoscopically not accessible necrotic areas may require minimally invasive or open surgical approaches[16].

OPEN SURGERY

AP can lead to severe complications, such as hemorrhage, perforation, or ischemia. These complications may require immediate open surgical treatment. Abdominal compartment syndrome is a further severe potential complication of AP that must be managed *via* laparotomy. The drainage or debridement of ANCs and contacting the omental bursa should be avoided during these surgical emergency procedures [58]. Beside emergency indications, INP itself is a well-accepted indication for surgical treatment[59].



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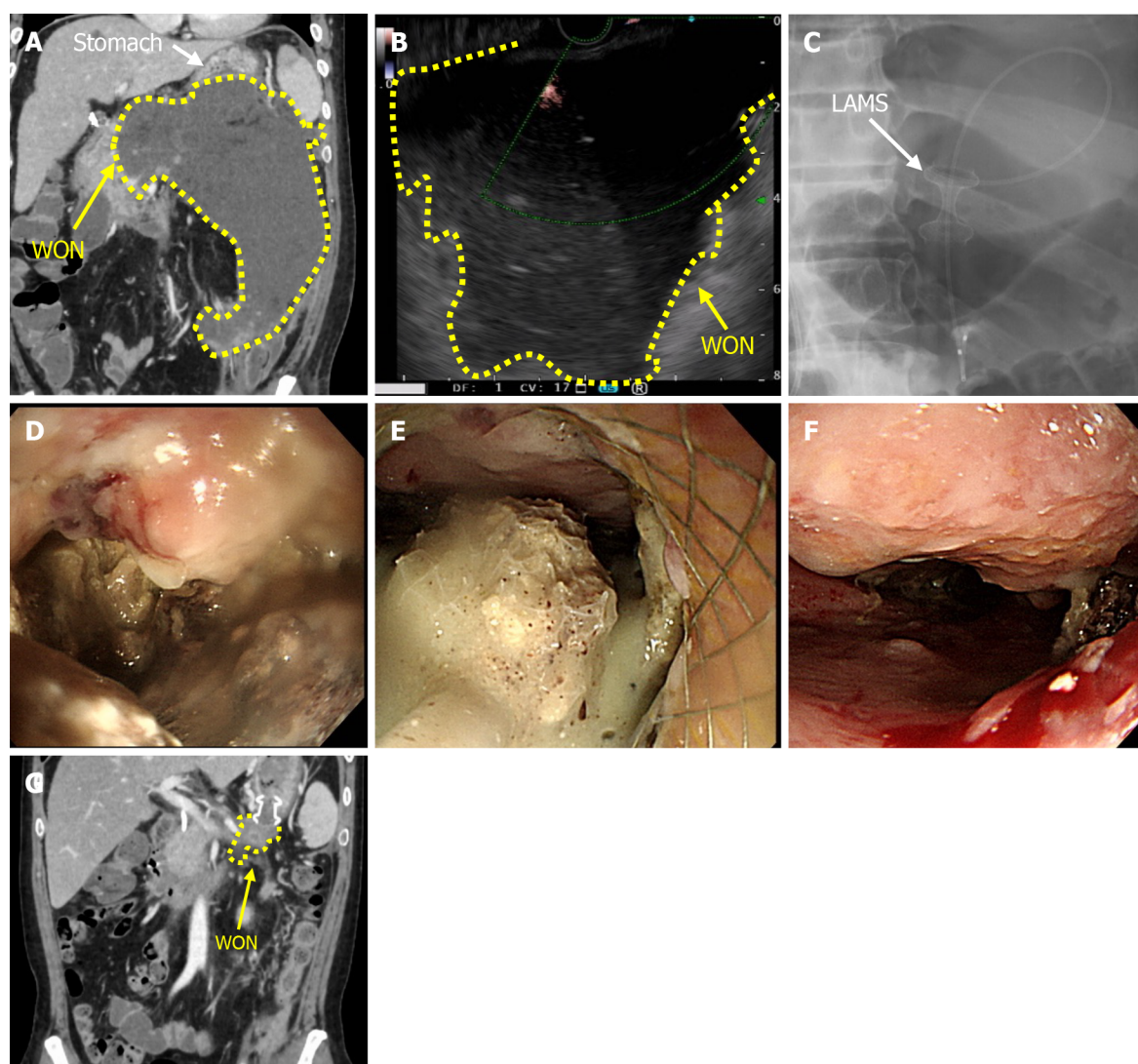
Figure 2 Endoscopic transluminal drainage with plastic stenting. A: A typical computed tomography (CT) scan with walled-off necrosis (WON) formed by necrotizing pancreatitis (white arrow shows stomach and yellow dotted line is the demarcation line of the WON); B: Endoscopic ultrasonography (EUS)-guided drainage for WON was performed (orange arrow shows the needle of 22-gauge EUS needle); C: Two plastic stents and nasobiliary drainage tube was placed into the WON; D: The size of the WON was reduced in the CT scan one month after the procedure. WON: Walled-off necrosis.

Open surgical necrosectomy follows the main principle of exposing the necrotic area and bluntly debriding necrotic tissue: Necrosectomy can be performed with: (1) Open packing; (2) Closed packing; (3) Closed continuous lavage; and (4) Planned re-laparotomies. Open packing involves packing the necrotic cavity with non-adherent dressing after surgical necrosectomy. Readmissions follow every 48 h until the abdomen can be closed after inserting drains. Closed packing is performed when multiple, large, gauze-filled Penrose drains are placed in the residual cavity after necrosectomy and the abdomen is subsequently closed. Closed continuous lavage is performed with the help of two or more double-lumen Salem sump tubes and single-lumen silicone rubber tubes, which are inserted from each flank side and have an in- and outflow of the lavage. Up to 40 L of lavage fluids are used. Planned re-laparotomies provide continuous removal of necrotic tissue over several following days. Surgeons often incorporate zippers into the abdominal wall facilitating repetitive surgical intervention[59].

The standard surgical access is performed either as a transperitoneal or retroperitoneal access. Transgastric access has been added more recently and is considered a fast single-stage option for the treatment of symptomatic WON in severely ill patients[60]. A recent study suggested choosing surgical transgastric necrosectomy whenever feasible in the case of a disconnected pancreatic duct, for dense and large necrosis, and if cholecystectomy must be performed. If the transgastric access is not possible, the authors suggested video-assisted retroperitoneal debridement (VARD) as an alternative procedure[61].

MINIMALLY INVASIVE SURGERY

The main procedures of minimal invasive management of INP are minimal access retroperitoneal pancreatic necrosectomy (MARPN) and VARD. MARPN involves the placement of a 12-French catheter under CT guidance by an interventional radiologist prior to surgery. The preformed access tract is then dilated up to 30-French during the minimal invasive procedure, so that a rigid nephroscope can be entered. The nephroscope serves as visualization instrument and working channel for necrosectomy at the same time. An irrigation drainage system for continuous lavage is installed at the end of the procedure. MARPN can be done multiple times until the patient's condition improves.



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Figure 3 A case with endoscopic transluminal drainage with lumen-apposing metal stent. A: Computed tomography (CT) scan before performing the endoscopic ultrasonography (EUS)-guided drainage (White arrow shows the stomach and the yellow arrow shows the walled-off necrosis (WON); the yellow dotted line is the demarcation line of the WON); B: EUS (with color doppler) picture shows marked echoic lesion without vessels; C: Lumen-apposing metal stent (LAMS) and nasobiliary drainage tube were placed (white arrow shows LAMS: Hot AXIOS™ 15 mm × 10 mm, Boston Scientific, Marlborough, MA, United States; Boston Scientific Japan, Tokyo, Japan); D: Esophagogastroduodenoscopy was inserted into necrotic cavity through LAMS; E: Necrosectomy was performed using endoscopic retrieval net; F: Endoscopic findings of the WON one month after the multiple necrosectomy sessions (2-3 times/wk); G: CT scan shows marked reduction of WON cavity one month after multiple necrosectomy sessions. WON: Walled-off necrosis; LAMS: Lumen-apposing metal stent.

VARD consists of combined manual and laparoscopic necrosectomy. It was first reported in 2007 by van Santvoort *et al* [62], who described it as “a hybrid between pure endoscopic retroperitoneal necrosectomy and the open translumbar approach.” The procedure starts with a left flank subcostal incision facilitating direct manual debridement followed by a laparoscopic deeper inspection and debridement by laparoscopic instruments. The intervention ends with a continuous lavage.

COMPARISON BETWEEN OPEN AND MINIMALLY INVASIVE SURGERY

Open surgical necrosectomy in AP was historically associated with a mortality rate of 50% or higher [63, 64]. Improved intensive care management, as well as advances in surgical techniques, including minimally invasive options, and the availability of first line endoscopic and minimally invasive procedures have improved patient outcomes over the past decades [65].

A retrospective study compared outcomes of INP patients between 1997-2008 and 2009-2013 and revealed decreased mortality (23.8% *vs* 11.2%, $P = 0.001$) and overall complication rates (73.3% *vs* 64.4%, $P = 0.80$) in the more recent cohort. Minimal invasive approaches contribute to better treatment success rates and improved outcomes in INP as compared to open surgery. MARPN also reportedly results in decreased postoperative multiorgan failure compared to open pancreatic necrosectomy (35% *vs* 20.4%, P

= 0.001)[66].

A recent retrospective cohort study comparing 88 patients with open surgical necrosectomy to 91 patients who were treated with minimal invasive surgery (MIS) showed that MIS results in a fivefold decrease in mortality[49]. A meta-analysis published in 2018 reported lower risk of death rates in the very high-risk group when comparing minimally invasive necrosectomy to open surgery[67].

STEP-UP APPROACH

The therapeutic approach in INP patients has shifted from open surgical treatment to a less invasive management that can be summarized by “three Ds”: Delay – drain – debride. This approach leads to the introduction of the so-called “step-up approach”, which was first described in 2006 by the Dutch Pancreatitis Study group in their PANTER trial[40].

Delay refers to the solidification and complete encapsulation of the pancreatic collection when WON occurs. This is presumed to optimize conditions for intervention, with a lower risk of bleeding and less reinterventions. Drain alludes to using a percutaneous or endoscopic transgastric catheter drainage to mitigate sepsis. Finally, when patients fail to show clinical improvement, debridement is required; in such cases, performing endoscopic or surgical necrosectomy is the next step[40]. A multidisciplinary team of INP experts can choose from different treatment options for each step and decides on the most suitable approach for each individual patient. Re-evaluation periods of 72 h between steps should be maintained[49]. This therapeutic management is also referred to as the “step-up approach”, which comprises both an endoscopic and a surgical approach. The overall paradigm is to start with the least invasive and harmful intervention with an option to escalate to more radical approaches with continuous evaluation. The step-up approach decreased the incidence of new multiple-organ failure from 40% to 12% when compared to primary laparotomy[40]. It is the current state-of-the-art approach and has been implemented in all major guidelines (Figure 4)[23,68].

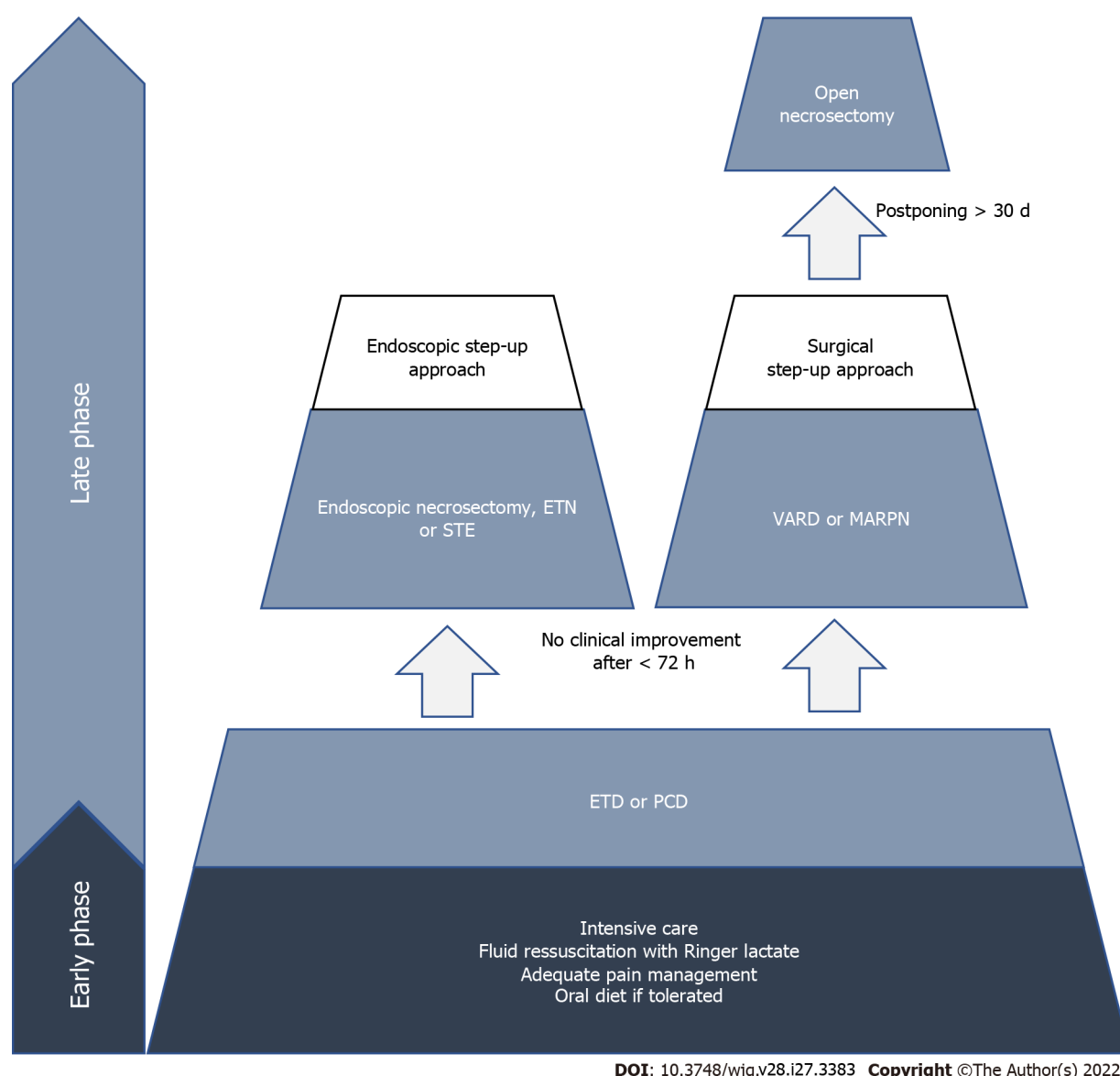
ENDOSCOPIC OR SURGICAL STEP-UP APPROACH

The step-up approach can be performed using endoscopic or surgical necrosectomy. Comparing both approaches has been subject of several randomized trials. From 2008 to 2010, the first prospective, multicentric randomized controlled trial comparing the surgical and endoscopic step-up approaches was performed in the Netherlands. The so-called PENGUIN trial compared endoscopic transgastric necrosectomy with prior retroperitoneal drainage and different techniques of surgical necrosectomy (VARD or, if not feasible, laparotomy) in 10 INP patients per group. The results demonstrated reduced inflammatory response as measured by serum interleukin 6 Levels, reduced rates of pancreatic fistulas (10% *vs* 70%, $P = 0.020$), and no occurrence of new-onset multiorgan failure (0% *vs* 50%, $P = 0.030$) in patients in the endoscopic arm[69]. The authors concluded that the endoscopic approach was associated with reduced physiological stress, while surgical access was more invasive.

The multicentric TENSION trial was conducted during 2011-2015 in the Netherlands and compared the outcomes of 51 patients following the endoscopic step-up approach to 47 following the surgical step-up approach. The findings showed no significant difference in mortality and major morbidity between both groups (43% in the endoscopic step-up approach *vs*. 45% in the surgical step-up approach, $P = 0.880$). However, the mean hospital stay was shorter (53 *vs* 69 d, $P = 0.014$), fewer pancreatic fistulas occurred (5% *vs* 32%, $P = 0.001$), and there was a lower overall mean cost (60228 € *vs* 73883 € in the endoscopic step-up approach group[70]).

From 2014 to 2017, the monocentric MISER trial was performed in the United States, comparing minimally invasive surgery (laparoscopic debridement or VARD) to the endoscopic step-up approach in a total of 66 patients. They included severely ill patient cohorts and excluded patients who had improved clinically with only percutaneous drainage as treatment. Consistent with the findings of the TENSION trial, MISER showed no difference in mortality rates (8.8% with the endoscopic step-up approach *vs*. 6.3% with minimally invasive surgery, $P = 0.999$). However, patients assigned to the endoscopic approach were less likely to develop enteral and pancreatic-cutaneous fistulas (0% *vs* 28.1%, $P = 0.001$), experienced a lower rate of major complications (12% *vs*. 41%, $P = 0.007$), and had lower rates of SIRS (20.6% *vs* 65.6 %, $P < 0.001$). Six months after treatment, patients in the surgical group had significantly more disease-related adverse events than did those in the endoscopic group (43.8 % *vs* 5.9 %, $P < 0.001$). Finally, the physical health scores for quality of life at 3 mo were better with the endoscopic approach ($P = 0.039$) and the mean total cost were lower (\$75830) compared with the surgical approach (\$117492)[49].

The currently available randomized controlled trials point to the endoscopic step-up approach as the preferred treatment for INP patients. However, if the endoscopic treatment is unfeasible, or the necrotic collection extends to the flank or pelvic region (which is difficult to access endoscopically), surgical interventions constitute the alternative when performed as a step-up approach. Each INP patient should be assessed and treated by a multidisciplinary team with sufficient experience in both approaches.



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Figure 4 Overview of the step-up approaches of infected necrotizing pancreatitis patients. In the acute phase, multidisciplinary treatment for acute pancreatitis is recommended. Endoscopic necrosectomy or surgical step-up should be considered if there no clinical improvement is observed within 72 h. Open necrosectomy should be considered after video-assisted retroperitoneal debridement or minimal access retroperitoneal pancreatic necrosectomy. ETN: Endoscopic transluminal necrosectomy; STE: Sinus tract endoscopy; ETD: Endoscopic transluminal drainage; PCD: Percutaneous catheter drainage; VARD: Video-assisted retroperitoneal debridement; MARPN: Minimal access retroperitoneal pancreatic necrosectomy.

TIMING OF INTERVENTIONS

The optimal timing of interventions remains a controversial topic and is subject to ongoing debate. An international survey performed in 2016 among 87 pancreatologists revealed that 55% of experts routinely postponed invasive interventions after diagnosing infected necrosis in AP and awaited the effect of antibiotics. However, 33% of pancreatologists preferred surgical necrosectomy as early as possible in infected necrosis, while the remaining 67% would select that route only in the case of WON [71].

A 2014 prospective study including 223 patients revealed that a postponed surgical intervention after 30 d was associated with a lower mortality rate compared to that associated with surgical intervention before day 30 [10% (9/87) *vs* 21% (28/136), $P = 0.040$] [72]. This study followed up on a retrospective study from 2007 that also revealed that patients receiving a postponed surgical necrosectomy exhibited lower mortality rates as compared to those receiving surgical treatment after 15-29 d and 1-14 d (8% *vs* 45% *vs* 75%, $P < 0.001$) [26].

A recent study of the Dutch Pancreatic Study Group, the POINTER trial, determined whether the outcomes in INP patients could be improved by early catheter drainage. In the study, catheter drainage was performed immediately in 55 patients, while 49 received the treatment after waiting until WON occurred. Patients were included when there was gas reported on CECT, positive gram/culture FNA,

and clinical suspicion for INP. The rate of organ failure was comparable in both groups and there was no difference in mortality rates. The total number of interventions was 4:1 in the early intervention group compared to the group with delayed intervention, and the total number of necrosectomies in the whole number of patients was 28 (51%) in the immediate as compared to 11 (22%) in the postponed drainage group. Postponing the intervention led to conservative treatment in nearly 40% of patients. This trial could not detect a benefit of immediate drainage over postponed drainage. Conversely, postponing intervention may ultimately avoid necrosectomy and its potential complications[73].

CONCLUSION

Recent advances in endoscopic and minimally invasive therapy have led to a shift in the interventional strategy for INP. Although no standardized approach suits every patient, the “step-up approach” has emerged as a paradigm to treat this severe disease. The key is to start with the least invasive procedure and potentially escalate to more invasive interventions after continuous evaluation, if necessary. This approach highlights the importance of a multidisciplinary team to guide therapeutic approaches in INP patients. The strategy should be based on the individual patient and should allow for dynamic changes in regard to the patient’s clinical condition. This claim is also backed by the studies presented in this review that demonstrate lower rates of new multiorgan failure and reduction of hospitalization days, among other preferred outcomes. Even with these recent advances, INP continues to elicit a high mortality rate and further research is required to optimize strategic approaches.

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FOOTNOTES

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