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Pancreatic necrosis: Complications and changing trend of treatment

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Abstract

Incidence of acute pancreatitis seems to be increasing in the Western countries and has been associated with significantly increased morbidity. Nearly 80% of the patients with acute pancreatitis undergo resolution; some develop complications including pancreatic necrosis. Infection of pancreatic necrosis is the leading cause of death in these patients. A significant portion of these patients needs surgical interventions. Traditionally, the “gold standard” procedure has been the open surgical necrosectomy, which is now being completed by the relatively lesser invasive interventions. Minimally invasive surgical (MIS) procedures include endoscopic drainage, percutaneous image-guided catheter drainage, and retroperitoneal drainage. This review article discusses the open and MIS interventions for pancreatic necrosis with each having its own respective benefits and disadvantages are covered.

Key words: Pancreatic necrosis; Necrosectomy; Open surgery; Minimally invasive surgery; Complications; Treatment; Review article

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Core tip: Pancreatic necrosis is one of the serious complications of acute pancreatitis. A significant portion of these patients needs surgical interventions. Traditionally, the “gold standard” procedure has been the open surgical necrosectomy, which is now being completed by the relatively lesser invasive interventions which include endoscopic

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drainage, percutaneous image-guided catheter drainage, and retroperitoneal drainage which are discussed in detail in this review article. However, no single modality is optimal for the treatment, and a multi-modal approach is needed. The mainstay of the management is now shifting to a “Step-up approach” from the most non-invasive towards the most invasive techniques in a step-up manner as the indications arise.

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INTRODUCTION

In the Western countries, acute pancreatitis is responsible for significant morbidity, high health care resources utilization and expenses. An unexplained increase in the incidence of acute pancreatitis has been noted in the past few decades in number of Western countries; ranging from 5 to 70 per 100000 persons per year^[1-3]. The rate of hospitalization has gone up reaching 0.7 per 1000 persons over the same period^[4]. Cholelithiasis and excessive alcohol intake are the leading predisposing risk factors, which collectively are responsible for nearly 2/3rd of the reported cases^[3,5-8].

Although majority of the patients (approximately 80%) with acute pancreatitis undergo resolution of symptoms, a minority of these cases (*i.e.*, approximately 20%) run an advance complicated course resulting in pancreatic tissue and/or peri-pancreatic tissue necrosis, which is accountable for considerable mortality and morbidity rates (reaching up to 27%)^[9]. Among these patients with necrotizing pancreatitis, infection of the necrotic tissue is the leading cause of death, which is a poor prognostic factor: pancreatic necrosis without infection has nearly 15% mortality rate while it is up to 30%-39% in those with infected necrosis. In approximately 1/3rd of the patients, the pancreatic necrosis gets infected at some stage of the clinical course^[10-12].

Bradley *et al*^[13] proposed, in the beginning of 1990s, that several patients with sterile pancreatic necrosis gets better without surgical intervention. Subsequently, the medical treatment of necrotizing pancreatitis was widely followed by the specialty. Despite this, a significant proportion of patients with pancreatic necrosis still need intervention. Open surgical necrosectomy was the traditional intervention for these patients, which is a highly invasive surgery resulting in 43%-89% complication rates and 9%-39% mortality rate^[14-19]. The “gold standard” intervention for infected pancreatic necrosis was open necrosectomy previously, which is now being competed and challenged by the relatively lesser invasive interventions. These minimal access interventions can minimize the surgical stress and hence its adverse effects on the patients’ outcomes. Comparatively lesser morbidity and mortality were observed in several case series of minimally invasive surgical (MIS) interventions for necrotizing pancreatitis, but these might be confounded by the inherent selection bias favoring the MIS approach^[20-23]. Three types of MIS interventions are used in necrotizing pancreatitis that included: (1) percutaneous image-guided catheter drainage (PCD); (2) endoscopic drainage (ED); and (3) retroperitoneal necrosectomy (RN). Percutaneous drainage (PCD) is the most frequently used first-line intervention in the management of necrotizing pancreatitis. In 55.7% of patients with necrotizing pancreatitis, PCD was the only and definitive intervention^[24]. RN has two fundamental types: (1) video-assisted retroperitoneal debridement (VARD); and (2) minimal access retroperitoneal pancreatic necrosectomy.

Treatment of necrotizing pancreatitis is evolving continuously. The open surgical approach (commonly used previously) is now being replaced by the MIS techniques, but the evidence supporting the superiority of these techniques is still insufficient and therefore further studies are needed to support the superiority claims.

Classification of acute pancreatitis

The Revised Atlanta Classification 2012 classifies acute pancreatitis in three forms as: mild acute pancreatitis characterized by no local/systemic complications (necrosis or pseudocyst) and organ failure (pulmonary/renal failure), moderate acute pancreatitis is characterized by temporary organ failure less than 24 h duration or local

complications, severe acute pancreatitis is described as the persistence of organ failure greater than 24 h^[25].

The absence of pancreatic tissue necrosis or peripancreatic necrosis on imaging study defines interstitial edematous pancreatitis. Necrotizing pancreatitis is grouped into three types as: (1) pancreatic necrosis; (2) extra-pancreatic necrosis; or (3) combination of both. All three types can be sterile or get infected.

Acute peripancreatic fluid collection: Fluid collection around the pancreatic tissue without any encapsulated wall or necrosis either parenchymal/peri-pancreatic on imaging studies within the first 4-wk of acute pancreatitis is called acute peripancreatic fluid collection.

Pancreatic pseudocyst: It is the persistence of APFC for 4-wk with the formation of a well-defined wall.

Acute necrotic collection: It is defined as the collection of fluid combined with the parenchymal or peri-pancreatic tissue necrosis within the first 4-wk of the disease.

Walled-off necrosis: It is the persistence of acute necrotic collection (ANC): over 4-wk with the development of a well-defined wall^[25]. A simplified version of the above facts is shown below:

APFC -----> 4-wk + Walled-off -----> PP
 APN -----> 4-wk + Walled-off + Necrosis -----> walled-off necrosis (WON)

Necrotizing pancreatitis complications and their treatment

Management of necrotizing pancreatitis complications depends on the severity, which is determined based on Revised Atlanta Classification, and the type of complications such as pancreatic pseudocyst (PP), infection, hemorrhage, abscess, fistulas^[25]. A multidisciplinary approach is mandatory for the treatment of complications with the implementation of either a conservative, interventional, or surgical approach.

Infection: Superimposed infection of the pancreatic necrosis is a serious complication and the major cause of increased death rates in severe acute pancreatitis. It has been found out that almost 80% of the deaths associated with acute pancreatitis are due to infected pancreatic necrosis^[26]. Infection of pancreatic necrosis heightens between 2-4 wk of the presentation; but may occur at any stage of the disease course. The commonly causative pathogens are the Gram-negative bacteria but other pathogens such as Gram-positive bacteria and multi-resistant pathogens have been found to be increasing in the incidence^[27].

Several clinical features and laboratory findings are indicative of infected pancreatic necrosis; new-onset fever, tachycardia, and elevating leukocytes. It is also associated with septicemia, systemic inflammatory response syndrome (SIRS) and organ dysfunction as disease progresses^[28,29]. Although detection of infection in the pancreatic necrotic tissue is very vital for the selection of appropriate treatment approach, it is quite hard to recognize the infection. The detection of gas due to gas-producing pathogens or a fistula to the stomach, small intestine, large bowel on the imaging studies is greatly indicative of the presence of infection but only detected in a small proportion of patients. Moreover, the existence of gas is not mandatory to label as infected necrosis^[30].

Prophylaxis: Meta-analysis by Wittau *et al*^[31] showed that prophylactic antibiotics are not effective in the prevention of pancreatic necrosis infection or decreasing the mortality, and thus, not recommended. On the other hand, mortality rate is lowered with prophylaxis, but no effect has been noticed on the incidence of pancreatic necrosis infection rates. Beta-lactam antibiotics are shown to decrease both the infection and mortality rates as compared to imidazole plus quinolone combination.

Bleeding: The enzymatic destruction of pancreatic and extra-pancreatic tissue occurs in necrotizing pancreatitis, which leads to the destruction of blood vessels and formation of pseudoaneurysms^[32]. This is responsible for the bleeding complication in NP, usually in the later stages of the disease. About 1% to 6.2% of NP patients are affected by this complication^[33,34]. Bleeding complications should be suspected when there is a sudden development of hemodynamic instability with the falling hemoglobin levels or formation of a new mass or bloody output from the pancreatic tissue drainage. Embolization of the vessels with angiography is the first-line treatment option while surgical intervention is only done in case of first-line treatment failure^[35]. Splenic vein thrombosis is also responsible for variceal hemorrhage in a minority (4%-12.6%) of patients^[35].

Acute compartment syndrome: Acute necrotizing pancreatitis (ANP) can result in extravasation and accumulation of fluid resulting in acute compartment syndrome (ACS)^[36]. The ACS affects 27% of ANP patients, with a mortality rate of 50%-75% despite the reasonable treatment and monitoring^[37]. Therefore, it is prudent and rather mandatory to keep a track of the intra-visceral pressures during the management of acute pancreatitis. An intra-vesical pressure greater than 20 cmH₂O accompanied by renal insufficiency or respiratory failure should prompt a suspicion for the ACS diagnosis^[38,39].

The ACS is a surgical emergency and urgent surgical decompression with laparostomy is required. This approach has been shown in an experimental porcine model, to improve the hemodynamics, renal and respiratory status of the patient with statistical significance^[40]. It must be performed within 6 h to achieve better outcomes^[40]. Initially, the ACS is managed medically through fluid restriction, intestinal decompression, improving abdominal compliance *via* curarization. In some cases, with high intra-vesical pressure greater than 25 mmHg associated with new-onset organ dysfunction, refractoriness to medical therapy and nasogastric and rectal decompression, in such cases the percutaneous drainage is mandatory^[41].

The minimally invasive techniques of decompression were shown to be superior to laparostomy in terms of mortality and complication rates in a retrospective study^[42]. The study found a lower rate of mortality in the ACS or early ANP-treated with minimally invasive drainage techniques vs. laparostomy (19% vs 53%, $P < 0.001$); and complication rates of 41 % vs 80% ($P < 0.001$). Anyhow these results should be interpreted carefully as the study groups were not comparable^[42].

Vacuum-assisted open abdomen has shown variable results; but bias is present due to the low ACS incidence in acute pancreatitis resulting in confusion about the various severity grades. The samples included in this meta-analysis were relatively small with inherent methodological faults, which did not allow the authors to devise any clear recommendations for the optimal timing and the appropriate invasive method to use.

The DECOMPRESS trial (Clin-icalTrials.gov, NCT00793715) is going on to evaluate the laparotomy with transient abdominal closure in comparison to the minimally invasive drainages without any surgery in the ACS patients. The sample size is going to be 100 enrolling at five different hospitals.

Gastrointestinal ischemia with perforation: Nearly 10% ANP is complicated gastrointestinal necrosis. A study of autopsy findings revealed 27% ischemic colitis in 48 patients with ANP. The diagnosis is made by contrast enhanced computed tomography (CT) of the abdomen and pelvis on suspicion which shows the absence of enhancement or even perforated wall. These perforations are the result of microvascular thrombosis that occurs due to the peri-pancreatic inflammatory response involving the microvasculature accelerated further by the ACS. A re-opening at 24-48 h after the initial surgery can be justified based on the risk for ischemia and perforation^[43].

The treatment for ischemia or perforation is surgical which is not clearly codified. Stoma is highly recommended in the after surgical resection. A lateral protective ileostomy is shown to avoid the resection when intestinal viability is doubtful. Ileostomy was found to prevent ischemia and its complications in a series of 30 patients^[44].

Clinical course of acute pancreatitis

Acute pancreatitis progresses to severe acute pancreatitis in two stages. *First stage* which occurs over 1-2 wk, is characterized by an inflammatory reaction leading to a SIRS, which is mostly sterile (*i.e.*, without any sepsis or infection). The SIRS is usually without any organ failure but may cause multi-organ dysfunction (MOD), if severe. The usual timing of pancreatic necrosis in severe acute pancreatitis is within the first 4-d and progresses over the next 2-wk^[45]. Earlier in the disease course, the SIRS may not be accompanied by pancreatic necrosis; but once organ failure develops, most of the patients have pancreatic necrosis as shown by the imaging studies^[46,47].

In the second stage or late-phase, which occurs after 2-wk, an anti-inflammatory state develops which promotes the development of infection due to the increased passage of bacterial pathogens through the intestinal wall leading to infected pancreatic and extra-pancreatic tissue and fluid collections. Mortality is increased at two-stages, early rise is due to the severe SIRS causing organ failure while the second rise occurs due to infection in the pancreatic necrosis and the fluid collections^[48-51].

DIAGNOSIS

Contrast-enhanced computed tomography

Contrast-enhanced computed tomography (CECT) is principally used in the management of acute pancreatitis after 3-4 d when the necrosis starts developing and the local complications which were not present on the initial presentation may start to develop. Its main purpose is the detection of pancreatic necrosis and the degree of its extension, and detection of complications like venous thrombosis and pseudoaneurysms^[45].

The CECT is not a very good predictor of the severity of acute pancreatitis so its use at the presentation is limited to situations where another differential needs to be ruled out. Other clinical and biochemical features are more reliably predictive of the severity^[52]. The CECT is the imaging study of choice for acute pancreatitis. The Revised Atlanta Criteria is profoundly dependent on the morphological features for the description of sequelae of acute pancreatitis and hence CECT is vital for it^[53,54].

Success of treatment is assessed by CT after percutaneous, endoscopic, or operative interventions. Side effects of the CECT are contrast induced kidney injury, radiation exposure and low sensitivity in the detection of necrosis in the setting of acute necrotic collection or WON^[52].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a good substitution for the CECT for detection of pancreatic necrosis^[52,55,56]. The MRI is used in cases where the CECT is not capable of detecting the gall stones in the common bile duct and to detect any solid necrotic debris in the fluid collections^[57]. Non-liquified components of the collections appear as homogeneous or heterogeneous on the CECT. MRI was the imaging study used in patients with a contraindication to the CECT, *e.g.*, allergic to intravenous (IV) contrast or pregnant patients^[58].

Non-contrast MRI is shown to be superior to non-contrast CT for the detection of pancreatic necrosis in patients with severe renal disease having glomerular filtration rate < 35 mL/min. The MRI is more sensitive and specific in detecting pancreatic necrosis as shown by Arvanitakis *et al*^[59]. The CECT is the imaging study of choice in majority of the institutions, but there are some institutions which opt for the MRI^[60]. The MRI has some other benefits such as non-ionizing radiations which are useful in the patients who are pregnant or need long-term surveillance^[56].

MANAGEMENT

Medical management

The medical management of pancreatic necrosis is primarily employed in the acute and sub-acute phases of the condition^[61]. The aggressiveness of the interventions depends upon the severity of the pancreatitis. Different scoring systems have been used to assess the severity of pancreatitis. These include, but are not limited to, Ranson's Criteria, SIRS response, and bedside index for the severity of pancreatitis score^[62,63]. Patients most at risk of developing necrosis are the ones who have a higher score on these indices. Based on the SIRS criteria, a patient presenting with SIRS response with concomitant renal dysfunction would need aggressive fluid replacement. The patient's overall clinical status should also be kept in view besides the clinical criteria.

Fluid replacement: In the acute phase of pancreatitis, body fluids should be replenished aggressively. Some evidence supports the use of ringer lactate as compared to normal saline in the early phase^[64]. Another review states that crystalloids and colloids have the same effect^[65]. Therefore, care should be taken during the replacement because the patient can have effusions on the imaging. The severity of the pancreatitis can be assessed by the amount of fluid required. Adequate fluid replenishment is associated with an improvement in the SIRS response in these patients^[66]. Measures of improvement can be assessed from the improvement of the vitals and urine output.

Alimentation: There is increased rate of catabolism in severe form of pancreatitis. Early nourishment is necessary to tackle malnutrition. The route of nutritional support in pancreatitis has been an area of interest for long-time. Studies have been conducted comparing alimentation through the parenteral, enteral and oral routes^[67]. There are concerns that oral intake leads to increased exocrine secretion of the pancreas. Generally, oral nutrition can be given in the absence of nausea, vomiting, and progressively rising pain in the abdomen. Diet low in fat should be used^[68]. Studies have shown that enteral nourishment by means of nasojejunal tubes do not lead to stimulation of exocrine secretions in the pancreas^[69]. Furthermore, enteral

nutrition helps maintain the gut barrier^[70]. There can also be benefit to the use of probiotic supplements^[71].

Supportive management: Patients with severe acute pancreatitis may have to be put on a ventilator. Pain should be managed with narcotics through the IV route. Mobilization, physical therapy, and changing positions are the valuable components of the supportive care.

Invasive treatment approaches for infected necrosis

Settings in which intervention is indicated: Timing of intervention is crucial to the effective and safe treatment of infected pancreatic necrosis. Pseudocyst must be differentiated from the walled-off pancreatic necrosis since their management and prognosis widely differs. Necrotic debris are better detected by the MRI and endoscopic ultrasound (EUS) as compared to the CT scan^[45]. Pseudocysts are fluid filled cysts outside the pancreas while the pancreatic necrosis contains cyst within the pancreatic parenchyma which contains solid debris.

Acute fluid collections do not require any intervention in most cases of the early stages while in the later stages, it may require intervention if symptomatic (*i.e.*, causing pain or intestinal obstruction). Infected necrotic collections need to be preferably drained radiologically or endoscopically in order to avoid or delay surgical intervention^[45].

WON needs no intervention if asymptomatic with any size and progression. They are likely to resolve without any intervention. In case of symptoms due to infection, pain or visceral/bile duct obstruction, intervention is needed.

Infected pancreatic necrosis: Intervention either endoscopic or surgical is only indicated in the first couple of weeks of acute pancreatitis onset, if infected pancreatic necrosis is detected in association with the worsening clinical condition and septicemia. However, no intervention is indicated in case of aseptic necrosis with the worsening clinical condition even with maximum medical treatment, unless infection is detected. The outcomes in these patients are rather poor with or without surgical intervention^[72,73]. Therefore, the recommendations are to delay the intervention up to 3-wk. Earlier debridement before 3-wk is associated with adverse outcomes. Several reasons are described for this approach. Firstly, the risk of bleeding is increased. Secondly, the necrosis becomes more prominent at the delayed stage, which helps in identifying the necrotic tissues during debridement, and thus minimize damage to the normal pancreatic parenchyma. This is responsible for long-term improved outcomes with respect to the endocrine and exocrine pancreatic functions as well as lesser post-operative complications^[71,74,75]. The most important thing to take care of at this stage is the detection of pancreatic necrosis, which in turn, will guide the further treatment line.

CT with contrast is now becoming the recommendation for the diagnosis of pancreatic necrosis and its timing is important. As compared to earlier CT imaging previously, the new recommendations are that CT with IV contrast should be delayed^[76]. There are a couple of reasons behind this approach. Firstly, this delayed CT is not only cost effective, but avoids radiation side effects. Secondly, CT with contrast accurately identifies patients who are likely candidates for the intervention. CT shows the extent of necrosis, which in turn, predicts the probability of getting infected, and thus, helps in stratifying patients for the intervention. Likelihood of infection decreases with 30% or less area of necrosis while the probability is higher for 50% or greater area of necrosis involved^[77].

Numerous studies have confirmed the benefits of delayed surgical intervention in the management of pancreatic necrosis^[78,79]. The International Association of Pancreatology Guidelines recommend delaying of the surgical treatment for 3-4 wk. A lower rate of mortality and morbidity has resulted from this approach as compared to the earlier intervention^[78]. A randomized controlled trial by Mier *et al*^[75] demonstrated higher mortality and morbidity incidence with early necrotic tissue resection within 3-4 d as compared to delaying to 12 d after the acute pancreatitis onset. Early surgical intervention is a non-partisan indicator of adverse sequel^[79].

Clinically stable patients with infected necrosis can be managed with non-invasive medical treatment (*i.e.*, antibiotics alone). This has been well demonstrated in a series of studies by different investigators^[80-84].

Different approaches for the invasive interventions

Two main approaches for the intervention are: Open surgical and minimally access techniques. The open surgical includes laparotomic trans-peritoneal or retro-peritoneal approach while the minimally invasive approach comprise of percutaneous, laparoscopic, retro-peritoneal, endoscopic transmural, or combined.

Delay before performing surgery

It is best to wait for a period of 4-wk before performing the surgery so that the infection and collection walls-off to an extent. Failure to do so, may lead to peritonitis, thus potentially affecting the morbidity and mortality^[75]. One study included 167 patients, who underwent necrosectomy^[15]. The mortality rate for the patients who underwent surgery more than 28-days after the onset of symptoms was compared with the patients who had the operation in the first 4-wk. The mortality rate was 5% for the former group *vs* 20% for the latter^[15]. It is therefore recommended to wait for 4-wk in the current guidelines^[24,79].

Open necrosectomy

Historical perspective: Historically, the surgical treatment of pancreatic necrosis was proposed in 1886 by Senn suggesting that beneficial outcomes for the patients undergoing removal of pancreatic and peri-pancreatic necrotic tissue^[85]. Since then, surgical treatment of pancreatic necrosis remained the standard, and the surgical techniques kept evolving during this time-period until 1990s when Bradley and Allen^[13] proposed that recovery is seen in several patients with aseptic necrotic pancreatic tissue treated with non-surgical treatment only. This led to the adoption of medical treatment as a general approach with surgical intervention reserved only for the individuals with infected necrosis^[13]. Debridement and drainage are most beneficial in cases of pancreatic necrosis, which have been secondarily infected and have been confirmed by performing bacterial cultures or suspected strongly^[12].

Approaches for necrosectomy: Necrotic tissue debridement *via* open surgical approach has long been the standard of care for infected pancreatic necrosis. This approach permits the scrutiny of the abdominal cavity to identify the necrotic lesions and clean them up as much as possible at the expense of considerable morbidity and mortality of 34%-95% and 11%-39%, respectively^[86]. Either a midline or bilateral subcostal approach is used while a transmesocolic approach can be used as a substitute in case of trouble. These approaches allow revelation of the lesser sac and pancreas. Care must be taken during the debris clean-up to avoid any compromise of the nearby structures^[87]. Several samples for bacterial cultures are vital to take. A suggestion by several authors is that in order to avoid abdominal compartment syndrome and to make the repeated debridement easier after the surgical intervention, leaving the abdomen opened might help. In case of abdominal closure, two approaches are proposed: (1) "Close Packing technique" in which the abdomen is packed closed with a drain placed that permits the repeated reopening for debridement; and (2) "Extended Irrigation technique" which is achieved by abdominal closure with the placement of draining catheters for continuous irrigation in the lesser sac, retroperitoneal location, and posterior to the colon^[45].

Which technique is better? Several studies have shown the superiority of the closed packing technique, which was introduced by the Fernandez del Castillo *et al*^[88] in 1998. They showed that post-operative closure with packing and irrigation technique is associated with lower mortality and morbidity rates and the need for repeated reopening. A series proved these findings in 2008^[15,88]. The Werner *et al*^[89] review explained the lower incidence of morbidity and the need for re-visiting the operating room for re-laparotomies. A retrospective study ($n = 244$) showed superiority of the drainage/lavage in terms of decreased mortality^[90]. In spite of these studies, the superiority of these techniques over the repeated laparotomies approach is based on the limited evidence^[45].

Disadvantages of open necrosectomy: Open necrosectomy is associated with high morbidity and mortality^[86]. Complications that could occur in the early post-operative period are perforation of viscus, organ dysfunction, bleeding, and wound infection. The late post-operative complications include: fistulas (pancreaticocutaneous and enterocutaneous), pancreatic insufficiency and hernias of the abdominal wall. Repeated laparotomies intensify the local and systemic injuries and has unfavorable impact on the hemodynamic status and the systemic inflammatory response. Abstaining from the surgical re-interventions lowers the morbidity but has no effect on the mortality rate^[75].

Advantages of open necrosectomy: Open necrosectomy has several advantages. Firstly, it facilitates the access to all the regions of the abdominal cavity with the necrotic tissues. Secondly, it permits the simultaneous cholecystectomy and choledocholithiasis management. Lastly, feeding jejunostomy could also be performed.

Necrosectomy via retroperitoneal approach

Although due to the difficult surgical pathway, retroperitoneal open necrosectomy is infrequently performed. It is the preferred technique for the patients requiring repeated operations and is associated with lower mortality rates in comparison with the anterior approach. Its main limitation is inability to give access to most of the peritoneal cavity^[91].

A 10-15 cm long incision along the length of the 12th rib in the left lateral sub-costal region is given with the patient in the right lateral decubitus position. In order to reach the pancreatic bed, dissection is performed posteriorly to the colon and mesocolon and anteriorly to the kidney to reach the Toldt fascia. The different pancreatic and peri-pancreatic regions are then cleaned-up blindly of the necrotic debris. Drain is placed to perform the repeated lavages^[92].

Trans-peritoneal laparoscopic necrosectomy

This approach was suggested by Parekh^[93] in 2006. Four of the 18 patients who underwent laparoscopic necrosectomy subsequently needed open surgical intervention. In this study, 11% mortality and 58% morbidity rates were observed^[93].

Due to the infrequent application of this approach, its comparison with other approaches is rather difficult. Lower complication rates were observed in a retrospective study evaluating the laparoscopic approach with open surgical approach favoring laparoscopic approach in terms of the occurrence of post-operative pancreatic fistula, blood loss, and average hospital length-of-stay (LOS) post-operatively^[94]. Recently, a series by Mathew *et al*^[95] showed that laparoscopic necrosectomy is a potentially safe and promising intervention having all the advantages of the minimally access approaches with a lower incidence of morbidity and mortality in contrast to the open surgical approaches.

Trans-peritoneal laparoscopic enteric drainage is performed by developing an anastomotic connection between the WON and the stomach or small intestine. This intervention is a single operation mostly; but recommended to be performed by the expert minimally invasive surgeons and a distinct WON near the stomach or the small bowel must be present^[96].

Minimally invasive interventions

Necrotizing pancreatitis is now approached with a changing treatment strategy favoring delayed surgical intervention whenever possible^[72]. Development of MIS approaches such as percutaneous, endoscopic techniques and other MIS interventions are providing substitutes for the morbid approaches like open surgery for necrotizing pancreatitis and walled-off pancreatic necrosis^[97-103].

Minimally invasive retroperitoneal approach

An endoscope or a laparoscope is passed into the retroperitoneal space through a radiologically-guided percutaneous tract into the necrotic tissue collection. This is followed by the necrotic debridement and lavage. A series by van Santvoort *et al*^[98] showed that no more than three interventions were required, peri-procedural complications lower than 5%, with the morbidity and mortality rates of 10%-20% and 0-20%, respectively. Another series involving 400 patients noted a reduction in the rates of organ dysfunction and intensive care requirement after this procedure.

Radiologic percutaneous drainage

Radiologic percutaneous catheter drainage (PCD) was introduced in 1998 with the aim of obtaining fluid and tissue samples for bacteriologic culture and to drain the fluid collection in the necrotic area^[97]. The CT scan can determine the extent of area involved by the necrosis and can give precise details about the exact site, amount, possible communication and structures in the proximity. High resolution contrast enhancement MRI through its ability to define the composition of the necrotic collection (liquid content, necrotic sediment, clotted blood, big size debris) is useful to select the best technique for the drainage, and hence, increases the chances of effective drainage^[104]. The MRI is 67% sensitive and 97% specific in detecting the presence of a superimposed infection in the pancreatic fluid collections, which gives a weaker diffusion coefficient ($P = 0.031$).

It is performed in two ways: trans-peritoneal or retro-peritoneal. The retroperitoneal has the advantage of preventing peritoneal infection *via* contamination and enteric seepage^[97,98]. This technique is used either as a primary intervention or as an adjuvant technique with other modalities^[45]. Percutaneous technique is highly advantageous for the unresolved collections, sepsis control, initial intervention prior to the endoscopic or surgical interventions and post-invasive treatments to drain the left-over fluid collections^[45]. The drainage should be enhanced in case of no resolution after 72 h. Optimization of drainage is done by increasing the drains caliber to 30F, using additional drains or using continuous drainage^[105,106].

Radiologic percutaneous technique has been shown to be effective primary intervention by a systematic review conducted by van Baal *et al.*^[24]. It was found to be effective in 55.7% of the patients with 15.4% mortality rate. No surgical intervention was needed in the successfully drained patients^[24]. The Dutch Pancreatitis Study Group evaluated percutaneous drainage in a randomized control trial (RCT), which showed 35% success rate^[107]. External fistulae developed in 27% of cases^[21,107]. **Table 1** includes literature report on PCD demonstrating complications and mortality in different studies.

VARD

The VARD usually follows percutaneous radiological drainage, performed through the same tract^[108]. A 5 cm incision is given in the 12th or 11th intercostal space after placing the patient in supine position. The location of incision is the same as that of the percutaneous radiological drainage. A lung grasper and a suction device are utilized for the necrotic debridement. Laparoscope is introduced retroperitoneally *via* the incision, which is followed by the insertion of two drains (large bore) *via* the incision with skin closure in between the drains.

Gastrointestinal fistulas, and peritoneal infection due to seeding during the dissection and bleeding complications are possible in these patients. A cohort of 639 patients with ANP were evaluated prospectively, which demonstrated a lower incidence of mortality and complications rate in the minimally access RN group as compared to the open necrosectomy wing (19% *vs* 38%, and 55% *vs* 81%, respectively)^[79]. Nearly 20% risk of the long-term pancreaticocutaneous fistula was found with the risk of progression to chronic fistula^[109].

Endoscopic necrotic debridement

In 1985, Ghebarde^[110] described per-oral trans-gastric endoscopic approach to PP drainage in. Subsequently, in 1996, Baron *et al.*^[111] explained the walled-off pancreatic necrosis irrigation *via* a nasocystic catheter introduced through the wall. In 2000, Seifert *et al.*^[112] performed the first endoscopic necrotic debridement of WON^[113].

Complications of retro-peritoneal approach, especially the pancreaticocutaneous fistula and the advancements in the endoscopic techniques are the reasons behind the increased attention towards the endoscopic approach. Endoscopic approach is preceded by a trans-gastric approach like the radiologic drainage before the retroperitoneal approach. In case of inefficiency of the endoscopic technique, surgery should be performed^[114].

Technique: The necrotic cavity is accessed *via* the insertion of endoscope through the mouth and then *via* the stomach wall to perform necrosectomy. The point of entrance through the gastric wall is identified from the bump produced by the necrotic collection from the outside in 50%-60% of the patients^[45]. In some cases, the bump is not visible due to different reasons such as the small sized collections, low serum levels of albumin, and collections in proximity to pancreatic tail. In such cases, in order to avoid damage to the structures in the proximity, EUS is used to identify the collection, determine its nature and guide the access. The benefits of EUS-guided endoscopic technique were evaluated in the RCTs by Varadarajulu *et al.*^[115] and Park *et al.*^[116], which showed higher success rate in the EUS-guided technique (> 95% *vs* 33%-66%) and low adverse events incidence (0%-4% *vs* 13%-15%)^[11,115].

The trans-gastric opening formed is dilated *via* a balloon followed by the insertion of two large bore double pigtail catheters. Necrosectomy and lavage is performed *via* a few instruments such as the basket dormia, forceps, and balloons, *etc.*, requiring 3-6 sessions to achieve a complete removal of debris.

Evidence supporting endoscopic necrotic debridement: Endoscopic necrotic debridement has shown promising outcomes. A systematic review by Haghshenasskashani *et al.*^[117] found that fully resolved collections resulted in 76% of patients with 27% morbidity and 5% mortality rates. In this systematic analysis study, characteristics of the patients were different in the series evaluated^[117]. The PENGUIN trial conducted by the Dutch Pancreatitis Study Group evaluated endoscopic trans-gastric debridement in comparison to the video-assisted RN in patients with infected necrosis. Lower rates of MOD (0% *vs* 50%, $P = 0.03$) and pancreatic fistula (10% *vs* 70%) with no change in mortality rate were observed. The number of interventions needed were greater in the endoscopic group (3 *vs* 1, $P = 0.007$). These results should be considered with caution as the sample size was small ($n = 20$), different C-reactive protein (CRP) levels between the groups and an unusually greater mortality rate of 40%.

A systematic review by Mowery *et al.*^[118] recommended endoscopic or radiologic drainage as initial intervention before proceeding to surgery in patients with infected

Table 1 Peer-reviewed literature reports on the clinical outcomes of patients undergoing percutaneous catheter drainage

Author/year/country	Ref.	No. of patients	Mortality	Complications	Mortality
Jones/2016/ United States	[123]	69	PCD	N/A	6.5%
Navarrete/2016/Chile	[124]	17	PCD	1 = stent fracture, 1 = leak, 4, 2 = bleeding, 1 = pseudoaneurysm, 1 = venous oozing	0%
Sugimoto/2016/United States	[125]	39	PCD	New onset organ failure 0 ¹ , 5 ² , enterocutaneous fistula 4 ¹ , 6 ²	16%
Russell/2017/New Zealand	[126]	85	PCD	N/A	12%
Sleeman/2011/United States	[99]	63	PCD	Internal fistula <i>n</i> = 14 (23%), bleeding <i>n</i> = 2	8%
Ross/2010/United States	[127]	15	PCD	Immediate post-procedure complications; tachycardia and hypotension (<i>n</i> = 2), late complication, parenchymal infection (<i>n</i> = 1)	0%
Van Santvoort/2010/The Netherlands	[98]	88	PCD	Organ failure <i>n</i> = 5 (12%) ¹ , <i>n</i> = 18 (40%) ² , systemic complication <i>n</i> = 0 ¹ , <i>n</i> = 1 (2%) ² , enterocutaneous fistula/perforation <i>n</i> = 6 (14%) ¹ , <i>n</i> = 10 (22%) ² , pancreatic fistula <i>n</i> = 12 (28%) ¹ , <i>n</i> = 17 (38%) ² , incisional hernia <i>n</i> = 3 (7%) ¹ , <i>n</i> = 11 (24%) ² , new onset diabetes <i>n</i> = 7 (16%) ¹ , <i>n</i> = 17 (38%) ² , pancreatic enzyme needed <i>n</i> = 3 (7%) ¹ , <i>n</i> = 15 (33%) ² , intraabdominal bleed <i>n</i> = 7 (16%) ¹	19%
Rocha/2009/United States	[128]	64	PCD	Infection 27% ¹ , 35% ² , 71% ³ , single organ failure 36% ¹ , 12% ² , 14% ³ . MOSF 64% ¹	12%
Becker/2009/Germany	[129]	7	PCD	Spontaneous duodenal perforation (1/7), pancreato-colonic fistula (1/7), fistula to the retroperitoneal space (1/7), spontaneous gastric bleeding (1/7), exocrine insufficiency (2/7)	0
Bruennler/2008/United Kingdom	[130]	18	PCD	N/A	22%
Cheung/2005/Hong Kong	[131]	8	PCD	Intestinal fistula to abscess cavity (4/8), left subphrenic fluid collection (1/8)	12.5%
Risse/2004/France	[132]	6	PCD	1/6 ¹ Post-operative peritonitis, 1/6 ¹ 40 °C fever 24 h, 1/6 ¹ insulin dependent DM, 1/6 ¹ Psuedocyst	0
Carter/2000/Scotland	[23]	10	PCD	N/A	20%
Freeny/1998/United States	[97]	34	PCD	N/A	N/A
Echenique/1988/United States	[133]	20	PCD	12/20 (renal failure × 2, bowel fistula × 10)	0

¹Indicates PCD associated variables.²Indicates surgical procedure associated variables.³Indicates endovascular approach associated variables. PCD: Percutaneous drainage; N/A: Not available; MOSF: Multiple organ system failure; DM: Diabetes mellitus.

collections (level III evidence). Another systematic review by Luigiano *et al*^[119] concluded that higher success rates with lower morbidity and mortality rates were found for the endoscopic techniques in comparison to the percutaneous and surgical approaches. A meta-analysis by Gurusamy *et al*^[120] concluded that very-low quality evidence exists in support of the endoscopic minimally access techniques over the video-assisted retroperitoneal approaches in terms of the lower adverse events in the former group; but the mortality rate remained unchanged. Another meta-analysis by Puli *et al*^[121] showed that endoscopic trans-mural necrosectomy is safe and effective in the drainage of WON but decision should be made by the advanced/expert endoscopist.

Currently, the TENSION trial is in progress, which is evaluating the “all endoscopic approach”, *i.e.*, endoscopic trans-gastric drainage followed by the endoscopic necrotic debridement (if necessary) in comparison to the “step-up approach” which consists of the percutaneous drainage followed by the VARD^[122].

Disadvantages: There are several limitations to this approach because more than one procedure is required, which are performed under sedation or general anesthesia, failure to quantify and manage greater quantity of necrotic tissue and the limited ability to debride deep retroperitoneal extension and the left-sided distal necrotic collections^[98]. Other technical limitations are the non-availability of the dedicated instruments, difficulty in suturing or stapling the bowel lumen with cavity, risk of damaging nearby vascular structures^[98]. The endoscopic necrosectomy is a risk-free and effective technique only in the setting of experienced endoscopists in the specialized centers.

Therefore, the conclusions of the above noted studies in favor of endoscopic necrosectomy are promising, and although no clear consensus exists, it should be the intervention of choice in setting of favorable anatomy, skilled and highly experienced endoscopists since it has lower morbidity rate and risk of chronic pancreaticocutaneous fistula. Table 2 includes various studies on endoscopic transluminal necrosectomy and mentions clinical outcomes, complications and mortality.

Step-up approach

The latest approach that is under evaluation for the treatment of necrotizing pancreatitis is the “step-up approach”. This approach came into practice because surgical intervention was associated with high morbidity and mortality rates, and various newer approaches such as the radiologic and endoscopic techniques became the components of this approach. Step-up approach is the step-wise introduction of different techniques when one technique fails to be effective for at-least 72 h. Indicators of positive response are the normalization of the organ dysfunction or betterment of at-least 10% in any of the two parameters such as: white cell count, body temperature, and CRP levels. Each step is managed by multidisciplinary coordination between the endoscopists, radiologists, surgeons, and intensive care specialists who put their efforts to delay the proceeding to the next step and lower the mortality at each step.

Evidence supporting the “step-up approach”: In 2010, a sample of 88 patients was evaluated in a multicenter randomized controlled trial named the PANTER trial^[98]. In these patients, retroperitoneal drainage preferably percutaneous radiologic drainage or second-line endoscopic technique was performed as the first-step. This was followed by the video-assisted RN in the setting of failure. Open surgery with continuous post-operative lavage was performed as the third-step in case of failure. The “Step-up group” was significantly better in the outcomes in terms of morbidity (40% *vs* 69%), new onset organ dysfunction (12% *vs* 42%), incisional hernias (7% *vs* 24%), and diabetes mellitus new-onset (16% *vs* 38%), respectively. Further, 35% participants in the “Step-up group” did not need necrosectomy. However, no difference in the mortality was found between the two groups^[98]. The authors concluded that the “step-up approach” reduced complications by lowering down the surgical insult in the weaker and debilitated patients. Removal of infected fluid was enough with no need for necrosectomy if the condition of the patient was improving, in fact 35% of patients needed percutaneous drainage alone^[98].

The “step-up approach” is summed up as the “3D’s approach” (*i.e.*, Delay, Drain,

Table 2 Peer-reviewed literature reports on the clinical outcomes of patients undergoing endoscopic transluminal necrosectomy

Author/year/country	Ref.	No. of patients	Modality	Complications	Overall successrate (%)	Mortality
Jones/2016/United States	[123]	69	ETN	N/A	N/A	6.5%
Oh/2016/Japan	[134]	25	ETN	20% (5/24), 4 self-limited abdominal pain, 1 minor bleeding	100% pain score improvement, $p = 0.001$	N/A
Sharaiha/2016/United States	[135]	124	ETN	Suprainfection $n = 3$, stent occlusion $n = 2$, stent migration $n = 4$, hemorrhage $n = 1$	N/A	0%
Huggett/2015/United Kingdom	[136]	19	ETN	Stent migration after necrosectomy 2/19, abdominal pain 1/19	N/A	26%
Schmidt/2015/Denmark	[137]	81	ETN	Death 1 (1%), bleeding from necrosis cavity 4 (5%), bleeding from transmural tract 4 (5%), pneumoperitoneum 4 (5%)	N/A	11%
Smoczynsk/2016/Poland	[138]	56	ETN	Transmural stent displacement $n = 1$, GI perforation $n = 1$	N/A	0%
Siddiqui/2015/United States	[139]	68	ETN	Infection $n = 4$, bleeding $n = 5$	N/A	0%
Kumar/2014/United States	[103]	24	ETN	0/12 vs 8/12 (bleeding, enterocutaneous fistula and infection)	N/A	0
Smith/2014/United States	[140]	17	ETN	Bleeding $n = 1$, sepsis $n = 1$	N/A	5.8%
Saxena/2014/United States	[141]	5	ETN	Pseudocyst $n = 1$, stent displacement $n = 1$	N/A	0%
Rische/2013/Germany	[142]	31	ETN	Perforation of colon ($n = 2$); stent dislocation to jejunum ($n = a$), bleeding ($n = 1$)	83%	9.6%
Siddiqui/2013/United States	[143]	14	ETN	3/14 (perforation, pneumoperitoneum, bacteremia)	N/A	7.1%
Ardengh/2013/Brazil	[144]	15	ETN	4 patients experienced bleeding (entry side ($n = 3$), inside cavity ($n = 1$), and worsening of infection (33.3%))	N/A	13.3%
Yasuda/2013/Japan	[145]	57	ETN	Bleeding ($n = 5$), perforation ($n = 3$), air embolism ($n = 1$)	75%	11%

Gardner/2011/United States	[116]	104	ETN	14/104 (Bacteremia, infected collection, moderate bleeding at puncture site, C. <i>diff colitis</i> , retrogastric perforation × 2, pneumoperitoneum × 3, balloon dilatation in retroperitoneum, massive bleeding during dilatation, periprocedural hypotension and cardiac arrest, anoxic brain injury, PEG site infection. bleeding (19/104)	N/A	5.7%
Varadarajulu/2011/United States	[146]	60	ETN	5/60	N/A	5%
Becker/2009/Germany	[129]	7	ETN	Spontaneous duodenal perforation (1/7), pancreatico-colonic fistula (1/7), fistula to the retroperitoneal space (1/7), spontaneous gastric bleeding (1/7), exocrine insufficiency (2/7)	N/A	0
Seifert/2009/Germany	[22]	93	ETN	Pseudocyst <i>n</i> = 11, bleeding <i>n</i> = 13, perforation <i>n</i> = 5, fistula <i>n</i> = 2, air embolism <i>n</i> = 2, multiorgan failure <i>n</i> = 2	80% Fairly satisfied	15.5%
Mathew/2008/United States	[95]	6	ETN	N/A	100%	N/A
Voermans/2007/The Netherlands	[147]	25	ETN	7/25 (bleeding). 1/25 (perforation of wall)	N/A	0
Schrover/2007/The Netherlands	[148]	8	ETN	Bleeding <i>n</i> = 1	N/A	12.5%
Charnley/2006/United Kingdom	[149]	13	ETN	N/A	N/A	15.3%
Bakker/2005/The Netherlands	[100]	20	ETN	New-onset diabetes 2 (22%) ¹ 3 (50%) ² , use of pancreatic enzymes 0 (0%) ¹ , 3 (50%) ² persisting fluid collections 2 (22%) ¹ 3 (50%) ² , pancreatic fistula 1 (10%) ¹ 7 (70%) ² , enterocutaneous fistula 0 (0%) ¹ 2 (20%) ¹ , new-onset multiple organ failure 5 (50%) ¹ 0 (0%) ²	N/A	10%

¹Indicates ETN associated variables.²Indicates surgical procedure associated variables. ETN: Endoscopic transluminal necrosectomy; N/A: Not available; PEG: Percutaneous endoscopic gastrostomy.

and Debride). The primary goal of the step-up approach is infection control either with or without the removal of the necrotic parenchyma. Patients presenting with severe ANP are diagnosed and treated with endoscopic or radiologic drainage of the infected necrosis. The intervention is selected based on the extent of collection and the expertise of the center. Necrosectomy is done in case of failure. The difference in the

operators and instruments at different centers has led to the recommendation that the technique with which the team feels most comfortable should be adopted.

CONCLUSION

The management of ANP is continuously evolving from the early open surgical intervention to the delayed surgical intervention, and now to minimally invasive techniques becoming the first-line interventions. However, no single modality is optimal for the treatment, and a multi-modal approach involving interventional radiology, interventional endoscopy, surgery, and nutrition is the mainstay currently. The mainstay of the management is now shifting to a “step-up approach” from the most non-invasive towards the most invasive techniques in a step-up manner as the indications arise. Therefore, the first-line intervention should be either radiologic or trans-gastric endoscopic approach while early surgery is avoided to prevent the adverse functional consequences. At the same time, an indication for emergency surgery should not be missed as this may potentially lead to increased mortality and morbidity.

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