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Necrotizing Pancreatitis: Step Up Approach

*Betsabé Reyes, Javier Padilla, Pilar Elena González
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Abstract

Acute pancreatitis (AP) is a inflammatory condition of the pancreatic gland with or without involvement of peripancreatic tissues and distant organs. The incidence of AP is 20–35 cases per 100,000 inhabitants per year, with an overall mortality of 2–10%. In recent decades the incidence of AP has increased globally. Most cases follow a mild, self-limiting course, but 10–20% of patients develop a severe form with systemic and local life-threatening complications of pancreatic and peripancreatic necrosis come about 20–40% of patient with severe AP and aggravate organ functions. The traditional approach to the treatment of necrotizing pancreatitis with secondary infection of necrotic tissue is open necrosectomy to remove the infected necrotic tissue. But this is associated with high rates of complications, death and pancreatic insufficiency. The benefits of sequential treatment in cases of infected necrosis (“Step an approach”) compared to traditional open necrosectomy, showing less morbidity and lower costs. The sequential treatment is an alternative to open necrosectomy, including percutaneous drainage, endoscopic (transgastric) drainage, and minimally invasive retroperitoneal necrosectomy. With this approach, up to 35% of patients can be treated only with drainage, to avoid necrosectomy and to reduce the percentage of complications. In this chapter we present the step-by-step approach.

Keywords: necrotizing pancreatitis, step up approach, acute pancreatitis, percutaneous, endoscopic, necrosectomy

1. Introduction

Acute pancreatitis (AP) is a inflammatory condition of the pancreatic gland with or without involvement of peripancreatic tissues and distant organs [1]. The incidence of AP is 20–35 cases per 100,000 inhabitants per year, with an overall mortality of 2–10%. In recent decades the incidence of AP has increased globally and is expected to increase even more. The most common cause is biliary lithiasis, which accounts for about 40–50%. The alcohol, predominantly in males, is the second most common cause, at over 30% and 10–25% the cause is unknown.

Most cases follow a mild, self-limiting course, but 10–20% of patients develop a severe form with systemic and local life-threatening complications of pancreatic and peripancreatic necrosis come about 20–40% of patient with severe AP and aggravate organ functions [2–6]. Infected necrotic tissue is defined as a gram positive of pancreatic or peripancreatic necrotic tissue obtained by means of

fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the fluid collection on contrast-enhanced computer tomography (CT). Suspected infected necrosis is defined as persistent sepsis or progressive clinical deterioration in the intensive care unit without documentation of infected necrosis. Failure of one or more organs occurs in 40% of these patients with pancreatic necrosis and on rare occasions it can also occur in cases without necrosis. Mortality amounts to 30% when infection of the pancreatic and/or peripancreatic necrosis is present [7].

The traditional approach to the treatment of necrotizing pancreatitis with secondary infection of necrotic tissue is open necrosectomy to remove the infected necrotic tissue. But this is associated with high rates of complications, death and pancreatic insufficiency. The studies show that death rates from open pancreatic necrosectomy are between 10–40% [8–10]. The management of AP has evolved greatly in recent years thanks to a better understanding of pathophysiology, the improvement of the therapeutic arsenal of intensive care units, nutritional support, conventional and interventional radiology techniques and surgical treatment. Recently, a randomized trial called “PANTER” very well designed study by the Dutch Pancreatitis Study Group, demonstrated the benefits of sequential treatment in cases of infected necrosis (“Step an approach”) compared to traditional open necrosectomy, showing less morbidity and lower costs [7]. The sequential treatment is an alternative to open necrosectomy, less invasive techniques, including percutaneous drainage, endoscopic (transgastric) drainage, and minimally invasive retroperitoneal necrosectomy. The importance of step up approach is that the first step is percutaneous or endoscopic drainage of the collection of infected fluid to mitigate sepsis and this step may postpone or even obviate surgical necrosectomy. If the drainage does not take to clinical recovery, the next step is minimally invasive retroperitoneal necrosectomy. With this approach, up to 35% of patients can be treated only with drainage, to avoid necrosectomy and to reduce the percentage of complications [7].

2. Clasification acute necrotizing pancreatitis

Before to describe the management of infected necrosis, we need to know the classification of acute pancreatitis [11, 12].

The severity of acute pancreatitis can be defined as mild, moderately severe, or severe according to the revised Atlanta classification (**Table 1**).

- Mild acute pancreatitis: absence of organ failure or local and/or systemic complications.
- Moderate acute pancreatitis: organ failure, and/or transient local or systemic complications that resolve within 48 hours maximum. Mortality in this group is less than 8%.

Mild acute pancreatitis	absence of OF or local and/or systemic complications
Moderate acute pancreatitis	OF and/or transient local or systemic complications <48 hours
Severe acute pancreatitis	OF and/or transient local or systemic complications >48 hours
Potentially severe acute pancreatitis	OF or warning pancreatic sign (Table 2)

Table 1.
Clinical classification of pancreatitis (OF: Organ failure).

- Severe acute pancreatitis: continued organic failure over 48 hours accompanied by local and/or systemic complications. Mortality in this group is 36–50%.
- Potentially severe acute pancreatitis: organ failure or a warning sign at the beginning of its evolution (**Table 2**), and therefore requires closer monitoring, to anticipate the development of transitory, persistent organ failure or pancreatic infection. The need to detect and treat patients who are developing organ failure with invasive resuscitation measures as early as possible has been demonstrated with a strong degree of recommendation and a high level of evidence.

There is another classification of AP severity that adds another step to the severity of these processes: Acute critical pancreatitis, in which persistent organ failure (OF) coexists with necrosis infection, described in 2012 by Petrov et al.

Classification according to radiological characteristics according to the Atlanta Classification:

- Interstitial o edematous pancreatitis: the pancreas is enlargement due to inflammation or edema. The pancreatic parenchyma shows homogeneous enhancement, and the peripancreatic fat usually shows some inflammatory changes. Besides there may be some peripancreatic fluid. The clinical symptoms of interstitial o edematous pancreatitis usually resolve within the first week.
- Necrotising pancreatitis: about 5–10% of patients develop necrosis of the pancreatic parenchyma, the peripancreatic tissue or both. Necrotising pancreatitis shows necrosis involving the pancreas and peripancreatic tissues and less commonly as necrosis of only the peripancreatic tissue or pancreatic parenchyma alone. The natural history of pancreatic and peripancreatic necrosis is variable, because it may remain solid or liquefy, remain sterile or become infected, persist or disappear over time. The presence of infection can be proved by extraluminal gas in the pancreatic and/or peripancreatic tissues or when percutaneous fine-needle aspiration is positive for bacteria and/or fungi on Gram.

Local complications of acute pancreatitis:

- Acute peripancreatic liquid collection: presence of peripancreatic liquid in the context of edematous interstitial pancreatitis. It occurs in the first 4 weeks

Characteristics of patient	Analitics parameters	Radiological Features	Forecast scales
Age > 50 years	BUN >20 mg/dl	Pleural Effusion	APACHE II >2
BMI < 30	Hematocrit >44%	Pancreatic collections or peritoneal free liquid.	Ranson-Glasgow >3
Deteriorate state of mind	Procalcitonin >0.5 ng/ml in the first 48 hours		
Comorbidity	Reactive C protein >150 mgl, or progressive elevation in 48 hours)		
Abdominal defense	Elevated Creatinine		

Table 2.
Warning pancreatic sign (BMI: Body mass index, BUN: Blood urea nitrogen).



Figure 1.

In the CT scan image we can see acute pancreatic collection without radiological signs of infection.

and is characterized by the appearance of homogeneous fluid adjacent to the pancreas and its fascial planes without the presence of a wall.

- Pancreatic pseudocyst: well-defined collection with a wall formed without a solid component that occurs after 4 weeks of oedematous interstitial pancreatitis.
- Acute necrotic collection: collection with a solid and liquid component that appears in the context of necrotizing pancreatitis and can affect the pancreas and surrounding tissues. It has no wall (**Figure 1**).
- Encapsulated pancreatic necrosis (Walled-off necrosis): is an acute necrotic collection, mature, encapsulated with a well-defined inflammatory wall, and which appears 4 weeks after the onset of necrotic pancreatitis. It is heterogeneous and can affect peripancreatic tissues.

3. Infected pancreatic necrosis

The most important consideration in treating local complications is to demonstrate the presence of infection.

Because the majority of patients with sterile pancreatic or peripancreatic necrosis can be treated conservatively, regardless of the size and extension of the collections.

Drainage in a sterile collection can produce iatrogenic infection, worsening the patient's prognosis. Could only be an alternative in those patients with persistent symptoms such as abdominal pain, duodenal obstruction or jaundice [13, 14].

Necrosis infection usually occurs within 2–3 weeks of the onset of BP. Successive CT scans should be performed according to the evolution of the patient and not in a programmed way. Early onset is rare, and should be suspected if SIRS persists or recurs after 10 days–2 weeks [15]. Therefore, the suspicion of infection will be made according to the bad evolution of the patient: fever, increase of leukocytes, elevation of



Figure 2.
CT scan image showing radiological signs of pancreatic necrosis due to the presence of gas in the acute necrotic collection.

PCR and/or procalcitonin, sudden resurgence or worsening of FO. This clinical evolution can be given by sterile necrosis, and it is often a challenge to differentiate whether we are dealing with an infected necrosis or not. Given this scenario, CT has high sensitivity to detect signs of infection (gas in the collection only appears in 12–22% of infected cases (**Figure 2**). However the signs of infection are usually sufficient to diagnose a secondary infection of pancreatic or peripancreatic necrosis. In case of diagnostic uncertainty, a positive gram stain or culture of the necrotic collection, obtained by transabdominal fine needle aspiration, may be necessary. However, the disadvantage of fine needle aspiration in this scenario is the false negative rate of 25% [16].

4. Management off infection of pancreatic necrosis

We present the management of acute pancreatitis with signs of infected necrosis. For this we will describe each of the therapeutic options in the philosophy of step up approach (Algorithm 1).

4.1 Antibiotic therapy

The first step is the administration of broad- spectrum antibiotic therapy [16]. The germs most involved are *E. coli*, *Enterobacter cloacae*, *Enterococcus faecalis* and *Bacteriodes fragilis*, and the antibiotic of choice for empirical treatment in these cases would be carbapenemics. In cases of allergy, quinolones would be used.

Recommended empirical therapy:

- Meropenem: 1 gr. e.v. every 8 hours
- Moxifloxacin: 400 mg e.v. every 24 hours

Once the final result of the cultivation is obtained, the anti-biotherapy will be adapted. A small proportion of patients can be managed with supportive care and antibiotics alone, without the need for additional invasive interventions [17].

4.2 The step-up approach

Open surgery in the treatment of infected pancreatic necrosis has been replaced by the minimally invasive approach. The multi-centre randomized clinical trial PANTER [18] showed that step up approach treatment of necrotising pancreatitis reduces patient mortality, multiorgan failure, costs and late surgical complications. The step-up approach consists of percutaneous catheter drainage or endoscopic transluminal drainage, followed by minimally invasive necrosectomy only when clinically required, is the current standard treatment [19].

4.2.1 Percutaneous catheter drainage

Secondary infection of pancreatic or peripancreatic necrosis can occur in the first 3 weeks after onset of disease, and long-term administration of antibiotics might lead to increased incidence of fungal infections and antibiotic resistance [15, 20]. The benefit of early drainage has been demonstrated, although its indication has to be established after confirmation of infection, otherwise we could be infecting a sterile collection. The ideal percutaneous drainage would be via the retro-peritoneal route and on the left side, which would facilitate subsequent minimally invasive surgical access if necessary. Current evidence shows that 35% of patients treated with percutaneous drainage in this phase will not require additional surgical necrosectomy and that up to 50% in series where a progressive increase in the diameter of the drainage catheter is used [19]. Once the radiological drainage was carried out, the therapeutic sequence would be as follows:

- if poor evolution persists after 48 hours and the patient's conditions permit it, a new drainage with a larger diameter would be attempted.

- if the poor clinical condition is maintained, despite the use of larger drains, surgical drainage should be carried out.

The current tendency is to be as non-invasive as possible. Several techniques have been described that will be developed in our service gradually, such as video assisted retroperitoneal access that presents significantly lower rates of abdominal complications than the most classic techniques. This technique uses radiological drainage as a guide to the collection, hence the importance of placing it on the left side as long as possible (**Figure 3**).

After 4 weeks, in addition to percutaneous radiological drainage in case of infection as mentioned above, endoscopic drainage could be evaluated. Generally, at this stage an inflammatory wall would already be formed consistent enough to withstand transgastric endoscopic drainage (walled-off necrosis).

4.2.2 Transgastric endoscopic drainage

The step-up approach can be done both surgically and endoscopically. The two different approaches have been compared with each other in two randomized trials. The first is the TENSION trial that concluded that the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death but the rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group [21]. The second trial is MISER [22] randomized controlled trial showed that an endoscopic transluminal approach for infected necrotizing pancreatitis, compared with minimally invasive surgery, significantly reduced major complications, lowered costs, and increased quality of life.

In short, the endoscopic staggered approach has become the approach of choice according to recent studies for the management of infected necrotizing pancreatitis [23–27]. However it could not be feasible in all patients. It depends

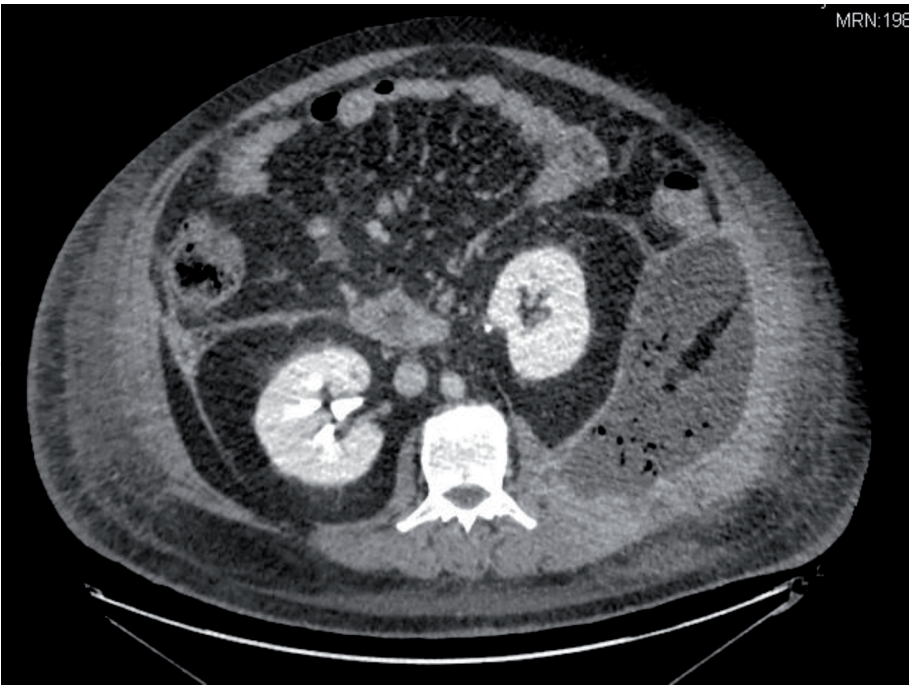


Figure 3.
CT scan image showing left retroperitoneal collection with easy access for percutaneous drainage. And it will allow a retroperitoneal laparoscopic approach.

on the anatomical location of the infected necrotic collections, availability of technique and experience of the center and trained personnel (**Figure 4**). The option of combined endoscopic transluminal and percutaneous catheter drainage, which is also known as dual-modality drainage, should not be overlooked in patients with large collections extending into the paracolic gutters or the pelvic region.

Currently, the stents placed between gastric light and the infected collection are metallic (**Figure 5**). They were created in 2011 and replaced with plastic stents. These stents provide wider light that allows better drainage and facilitates transluminal necrosectomy. The best available evidence comes from a randomized trial

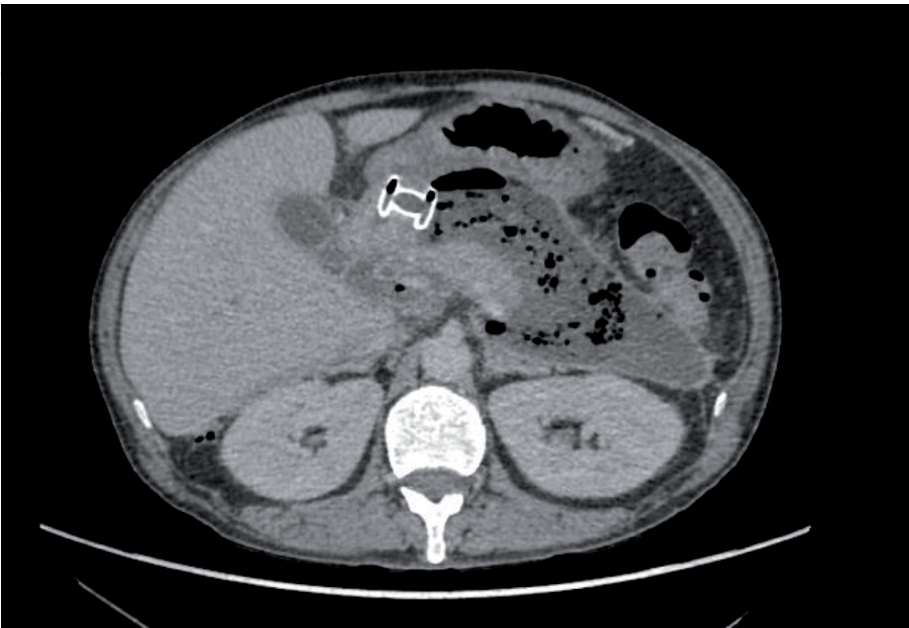


Figure 4.
CT scan image showing infected acute necrotic collection of retrogastric location. We can see metallic stent drainage inside the collection.

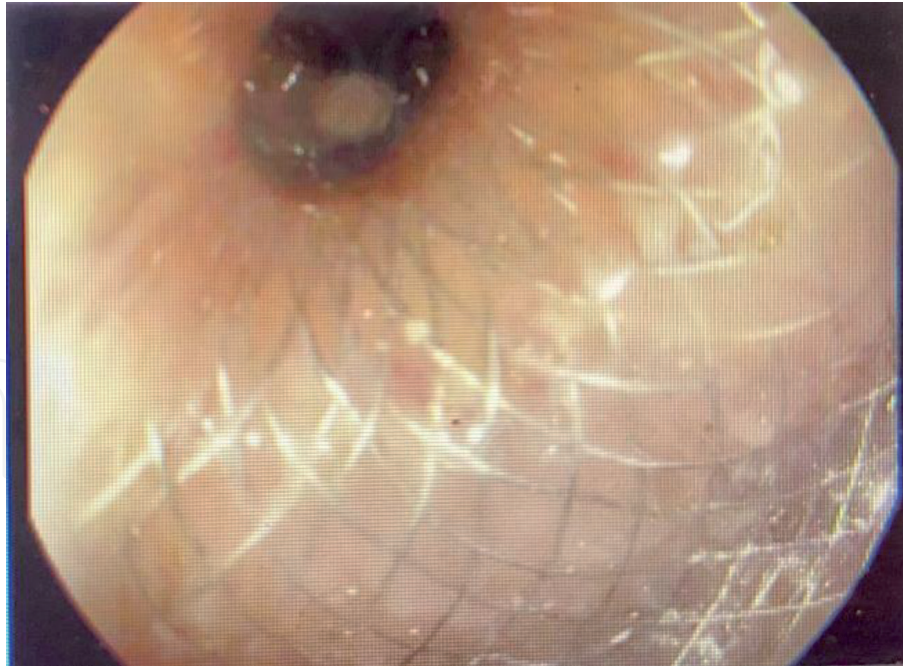


Figure 5.
Endoscopy image showing metallic stent that communicates the gastric camera and the acute necrotic collection.

that compared the efficacy of metal and plastic stents in the drainage of infected pancreatic necrosis. The study found no differences in the median number of procedures, readmissions, and length of hospital stay [28]. Although endoscopic treatment with metal stents was associated with higher procedure costs. In addition, adverse effects such as stent migration were observed. Therefore, the latest consensus guidelines recommend metal stents or double pigtail plastic stents for endoscopic transluminal drainage and removal after 4 weeks to minimize the risks of complications [28, 29].

4.2.3 Surgical necrosectomy

Between 23–47% of patients will improve only with percutaneous or endoscopic drainage. But in those patients with persistent disease, surgery is the next step [18, 30, 31]. Objectives of surgical debridement are to control the source of infection and reduce the burden of necrosis, while minimizing the proinflammatory damage of the intervention itself on the weakened patient. The current trend is to be as non-invasive as possible. We will start with a videoassisted retroperitoneal approach and if it is not enough we will perform necrosectomy by open approach [32].

4.2.3.1 Video assisted retroperitoneal debridement (VARD) in infected necrotizing pancreatitis

Several techniques have been described, such as video assisted retroperitoneal access that presents significantly lower rates of abdominal complications than the most classic techniques. This technique uses radiological drainage as a guide to the collection, hence the importance of placing it on the left side as long as possible. The tract formed by the anterior drainage is used to access the retroperitoneal space for intracavitary videoassisted necrosectomy (**Figure 6**). Traditional laparoscopic instruments are used under direct vision (**Figures 7 and 8**). We can leave well-positioned drains that allow washing. The process may be repeated if necessary to remove the infected pancreatic necrosis. It should be noted that the VARD approach

is more effective in treating central to left parietocolic infected pancreatic necrosis. However, it will be more difficult to access the necrosis located to the right of the mesenteric vessels [32] (**Figure 9**).

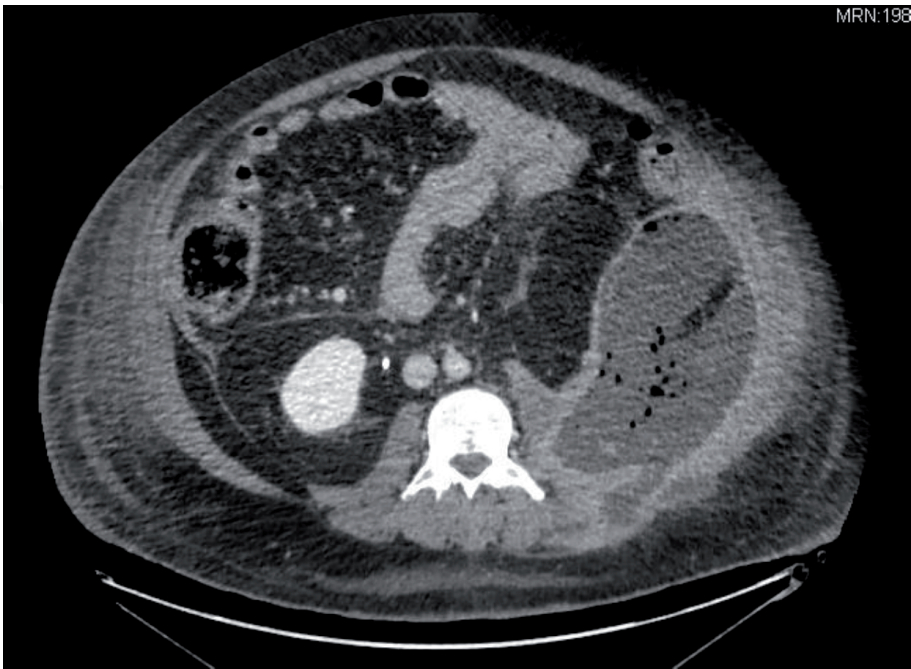


Figure 6.
CT scan image showing infected acute necrotic collection on the left flank. It allows a percutaneous drainage approach and subsequent laparoscopic retroperitoneal access.



Figure 7.
Using left retroperitoneal percutaneous drainage as a guide, we can access it by minimally invasive approach. We observed laparoscopic trocar through which we introduced camera, vacuum cleaner and laparoscopic tweezers.

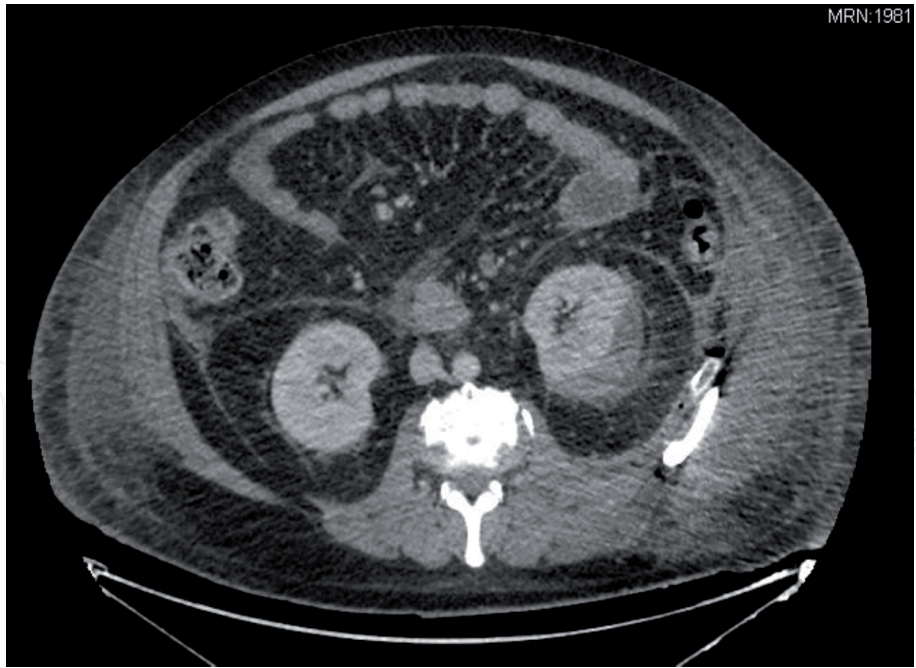


Figure 8.
Image of CT scan that objective retroperitoneal necrotic collection with drainage inside placed by laparoscopic retroperitoneal access.



Figure 9.
CT scan showing surgical drainage on the right flank by laparoscopic retroperitoneal access.

4.2.3.2 Surgical transgastric debridement

The concept is similar to endoscopic transgastric drainage. It can be performed by open or laparoscopic approach. An anterior gastrotomy is required to access the posterior face of the stomach and then the infected cavity. It is especially useful in central collections that do not affect the flanks (**Figure 10**). It is advisable to leave a drain inside the cavity for washing. There are studies of small sample size that demonstrate the efficacy of the technique with low morbidity [33–35].

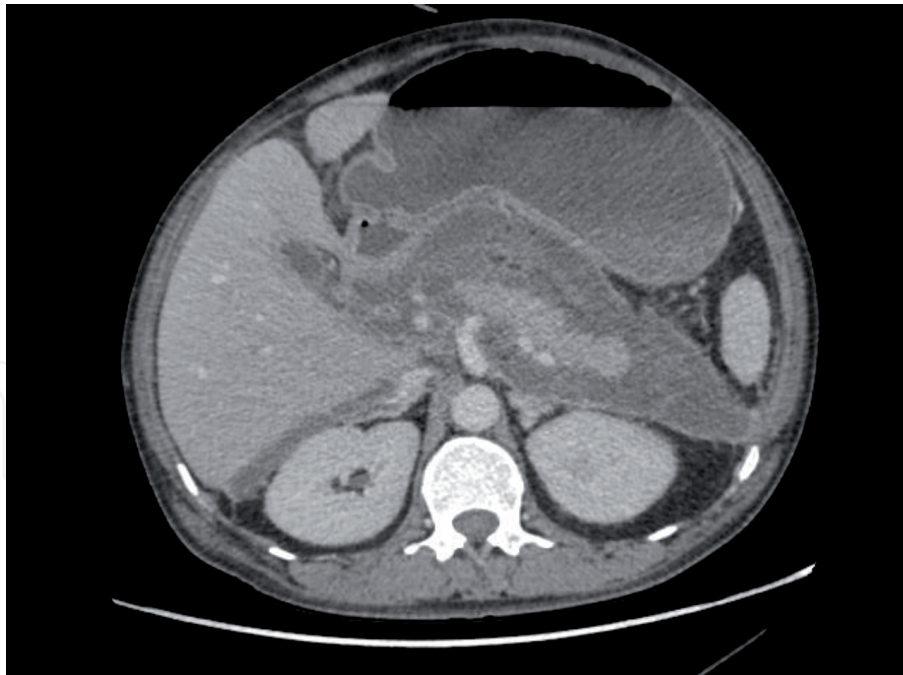


Figure 10.
CT scan image showing collection near the gastric posterior wall that would allow a transgastic approach.

4.2.3.3 Open surgical necrosectomy

If these methods are unable to control the infectious condition, the patient's deterioration, despite good drainage, including minimally invasive surgical drainage, would be indicated to the open surgical approach. The mortality of patients with infected necrosis is greater than 30%, as we have commented, the delay in surgery as much as possible will be more beneficial for the patient in terms of mortality and morbidity. Early debridement, and especially sterile necrosis, leads to a significant increase in mortality. Therefore, these techniques are reserved when everything else has not been enough [36–37]. We have widely described open necrosectomy techniques. None of them has been shown to be clearly superior to the other due to the lack of randomized studies, but the ones that offer the best results are:

- Open surgical necrosectomy with closed packing: described by A.L. Warshaw, with lower mortality rates than the other techniques (10%) and that would be indicated in limited necrosis.
- Open surgical necrosectomy with closed postoperative lavage: in case of more extensive necrosis. The recommended wash would be 12–24 liters every 24 hours with potassium-free dialysis fluid.
- Open surgical necrosectomy with open packing: it is the technique with the highest morbidity-mortality, but it would be indicated in cases with more extensive necrosis that exceed the colon.

Vacuum Assisted Closure therapy will be used as a temporary closure in cases where closure of the abdominal pare is impossible or in cases of abdominal compartment syndrome.

Current comparative studies, with the exception of randomized trials [18], should be interpreted with caution, given the severity of the often higher disease in

	Ramson	Glasgow
on admission	age > 55 yerars	age > 55 years
	white blood cell count>16.000 mm3	blood glucose>10 mmol/l
	blood glucose >200 mg %	LDH > 600 UI/l
	LDH > 400 UI/l	AST > 100 UI/l
	AST > 200 UI/l	serum urea>16 mmol/l
within 48 hours		Arterial PaO2 < 60%
		serum Calcium<8 mg/dl
		serum albumin<3,2 mg/l
		white blood cell count>15.000 mm3
	hematocrit fall>10%	
	blood urea nitrogen rise >5 mg%	
	Arterial PaO2 < 60 mmHg	
	base deficit>4 mEq/l	
	fluid sequestration >6 liters	
	serum calcium<8 mg%	

Table 3.
Ramson and Glasgow prognostic scale.

patients undergoing open debridement. Open debridement is indicated in patients with a high necrosis load that is diffusely distributed throughout the abdomen and that do not respond to staggered handling [32].

RAMSON: Prognostic scale in acute pancreatitis (**Table 3**).

GLASGOW: Prognostic scale in acute pancreatitis (**Table 3**).

Zero to do criteria met indicates mild pancreatitis; 3 or more criteria severe pancreatitis.

According to the number of criteria the rate of mortality is: 0–2 mortality >2%; 3–5 mortality 10–20%; 6–7 mortality 50–60%; > 7 mortality 70–90%.

5. Conclusions

Patients with diagnosis of acute necrotizing pancreatitis should be treated in centers with high experience by specialists in pancreatic surgery, endoscopists and radiologist experienced. It is essential the presence of a team of intensive doctors or anesthesiologists especially in the first weeks of evolution. Despite these measures the morbidity and mortality in these patients is still high, so we must try to reduce it with a correct management and applying the “step up approach”. The sequential treatment is an alternative to open necrosectomy, including percutaneous drainage, endoscopic (transgastric) drainage, and minimally invasive retroperitoneal necrosectomy. With this approach, up to 35% of patients can be treated only with drainage, to avoid necrosectomy and to reduce the percentage of complications.

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Conflict of interest

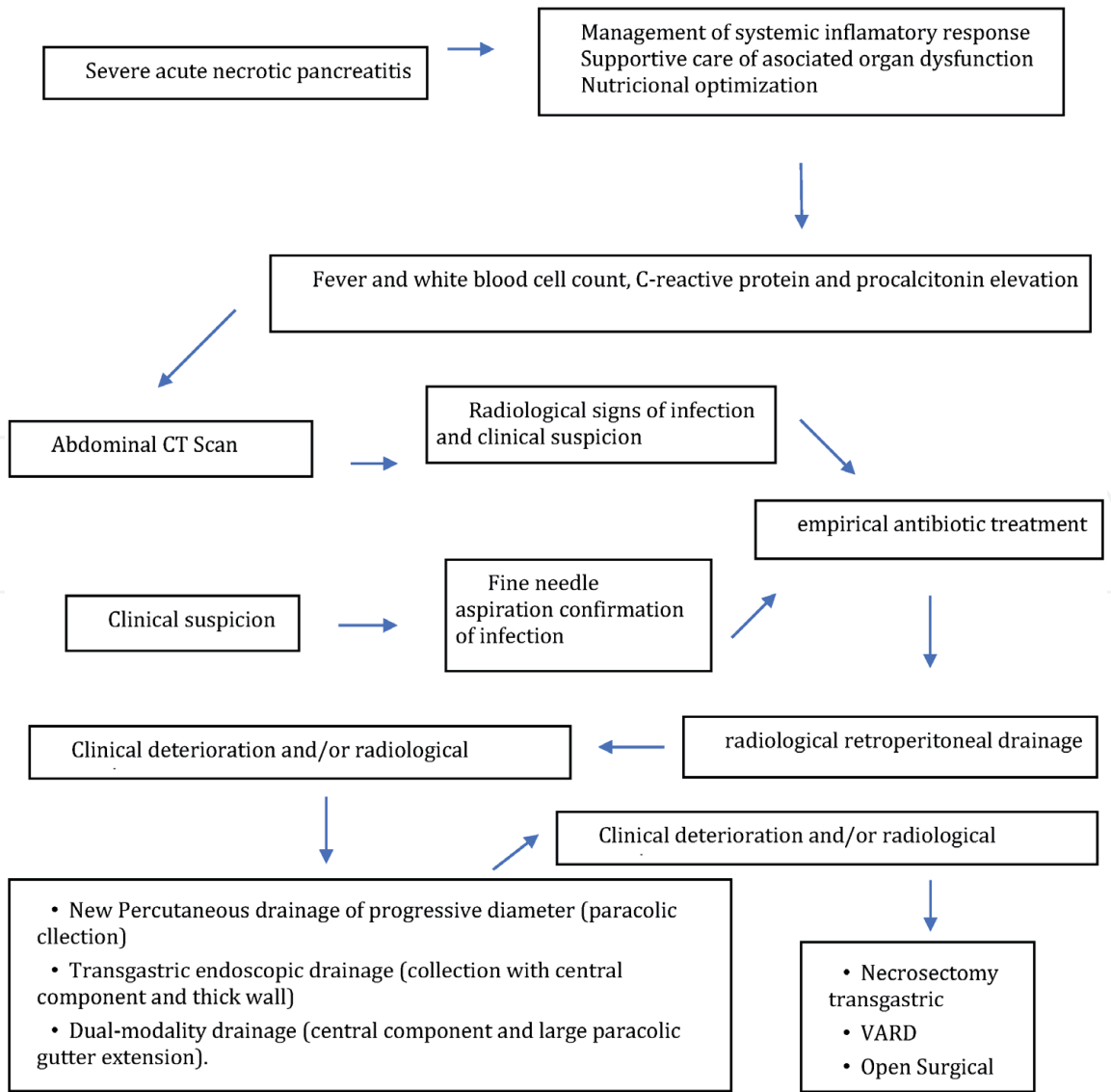
The authors declare no conflict of interest.

Notes/thanks/other declarations

None

Appendices and nomenclature

Algorithm 1. Management of acute pancreatitis with infected pancreatic necrosis.



AP	acute pancreatitis
Step an approach:	staggered approach
CT	computer tomography
OF	organ failure
BMI	body mass index
BUN	blood urea nitrogen
LDH	lactate dehydrogenase
AST	aaspartate ainotranferase
PaO2	blood pressure from oxygen
VARD	video assited retroperitoneal debridement
APACHE	acute physiology and cronic health evaluation (Figure 11).

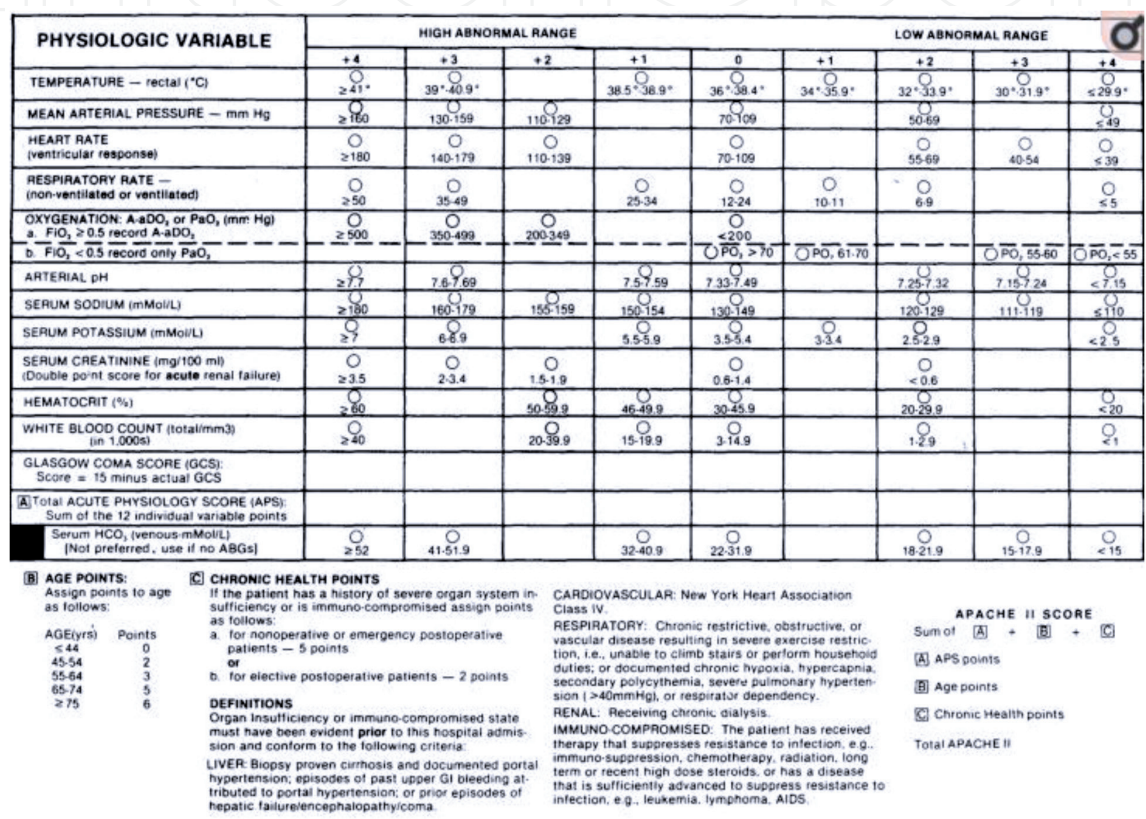


Figure 11.
APACHE SCALE. Health care Financ rev. 1984 Nov; 1984(Suppl): 91–105.

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