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REVIEW

Update: Role of surgery in acute necrotizing pancreatitis



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Laparotomy

Summary Acute necrotizing pancreatitis is a prevalent disease with high morbidity and mortality. The development of radiologic and endoscopic techniques to manage pancreatic necrosis commands a multidisciplinary approach, which has considerably decreased the need for laparotomy. The objective of this update is to define the role of surgery in the multidisciplinary approach to management of necrotizing acute pancreatitis.

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Introduction

The diagnosis of Acute Pancreatitis (AP) is based on the association of epigastric abdominal pain (typically through-and-through) and elevated levels of serum lipase above three times normal. The Atlanta classification, revised in 2012, should be used to guide management [1]. During AP, pancreatic necrosis may develop in the pancreatic parenchyma, in the peripancreatic tissues, or both, [2], constituting what is called Acute Necrotizing Pancreatitis (ANP). Currently, AP is classified in two evolutive phases: the early inflammatory phase associating signs of systemic inflammation and the late phase characterized by the onset of local complications (Fig. 1). Between 20 and 40% of patients develop Walled-Off Necrosis (WON), differentiated from pseudocysts, which are completely liquid, by Magnetic Resonance Imaging (MRI). Only 2 to 4% of WON will require surgical or endoscopic necrosectomy [3]. The Atlanta classification defines three degrees of severity for AP: (i) mild AP, absence of, local or systemic complications or organ

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failure; (ii) moderate AP characterized by either transient organ failure (less than 48 h) or local complications; and, (iii) severe AP, characterized by failure of one or several organ systems persisting more than 48 hours. Only 1/4 of patients with necrosis present signs of severity but in this setting, mortality is 98%, either secondary to infection of the necrosis, or to an acute complication such as gastrointestinal perforation or hemorrhage [4]. The prognosis of patients with ANP depends principally on two factors: the persistence of organ failure and secondary infection of pancreatic necrosis [5].

Traditionally, surgery was the only means to manage the acute complications related to severe pancreatic necrosis (ANP associated with organ failure persisting at least 48 h), representing 10 to 20% of all AP. However, morbidity and mortality were high. The development of less aggressive techniques with radiologic or endoscopic guidance, has limited the morbidity related to necrosis in patients with severe AP. The role of surgery in the management of ANP has thus evolved considerably during the last decades. The goal of this update is to define the role of surgery within a multidisciplinary strategy for severe ANP.

Treatment of pancreatic necrosis

When should pancreatic necrosis be treated?

Evolution of necrosis

Infection of necrotic collections is a major turning point in the evolution of patients with AP, occurring usually between the third and eighth weeks after onset. Mortality from infected necrosis, the main cause of death in AP, ranges from 30 to 35% [6]. The mechanisms of infection are multiple, including, by decreasing order of prevalence, iatrogenic, intestinal bacterial translocation, colonic micro-perforations with micro-vascular involvement [7], hematogenous contamination and, exceptionally, duodenobiliary reflux via pancreatic fistula. The prevalence of infected necrotic collections after surgical drainage increases from 25% during the first week to 60% during the first three weeks [8]. Lastly, the likelihood of a necrotic collection becoming infected increases proportionally with its volume [9]. Secondary infection of pancreatic necrosis should be suspected in the presence of CT scan changes or clinical degradation. For instance, the presence of air bubbles in undrained necrotic collections is strongly suggestive of anaerobic superinfection [10]. In patients who undergo operation for ANP with borderline hemodynamic status, about 40% have infected pancreatic necrosis on bacterial culture [11].

Indications for treatment of necrosis

The value of drainage and debridement has been established only for secondarily infected pancreatic necrosis [12], confirmed by positive pancreatic bacterial cultures, or strongly suspected (onset or persistence of temperature > 38.5°C, organ failure, the need of hemodynamic, respiratory and/or renal support, elevated or worsening white blood cell counts, increased C-reactive protein and/or discovery of bacteraemia). Percutaneous fine needle aspiration of peripancreatic collections to identify the presence of bacteria is not routinely performed [13]. The benefits of identification of the bacteria responsible for the infection and adaptation of antibiotic therapy are counter-balanced

by the risk of false negative results (up to 25%) [11]. Patients with infected collections or necrosis require an interventional approach to provide material for bacteriologic culture and therefore needle puncture is not useful. Strong clinical suspicion of necrosis infection and/or CT scan changes is elements that by themselves call for drainage; initial drainage techniques should not be surgical, if at all possible.

Delay before surgical intervention for necrosis

Surgery for pancreatic necrosis should be delayed for at least four weeks, in order for the collection to become "walled off" as much as possible and therefore prevent bacterial and chemical dissemination into the peritoneal cavity. Such contamination can lead to peritonitis, which strongly influences morbidity and mortality of patients who undergo operation [14]. Rodriguez et al. studied 167 patients treated by surgical necrosectomy. The mortality rate for patients undergoing operation more than 28 days after the onset of symptoms was 5% vs. 20% in the first four weeks [11]. One meta-analysis of eleven series totaling 1136 patients confirmed a statistically significant negative correlation between the duration of the interval before operation and mortality ($R = -0.603$; $P = 0.05$) [15]. The current recommendation is to wait at least four weeks [16,17].

How to treat pancreatic necrosis?

"Classical" surgical techniques

The objectives of treatment of pancreatic necrosis are to debride the devitalized tissues and drain all purulent collections.

Necrosectomy via laparotomy

Laparotomy has long been the rule, allowing exploration of the abdominal cavity to inventory the lesions and to remove as much infected necrosis as possible, accepting substantial associated morbidity (34 to 95%) and mortality (11 to 39%) [18]. The approach could be a midline or bilateral subcostal incision. The greater omentum is opened, exposing the lesser sac and the pancreas. In case of difficulties, the transmesocolic approach has been described as an alternative. Debridement is generally performed by manual fragmentation, taking care to respect the neighboring organs [19]. Numerous bacterial samples are necessary. Certain authors have proposed leaving the abdomen open at the end of the procedure to prevent the onset of Abdominal Compartment Syndrome (ACS) and to facilitate a "second look" procedure.

Upon closure, negative pressure wound therapy with the possibility of lavage allows continued debridement several days after operation. One non-randomized retrospective study evaluating 244 patients found that mortality was decreased owing to drainage/lavage after debridement [20]. In this study, pancreatic endocrine and/or exocrine insufficiency developed in half of cases requiring postoperative surveillance of pancreatic function.

Mikulicz sacs, filled with long prostate wicks and placed in contact, can be useful to buffer bleeding areas after necrosectomy and constitutes, for some teams, the first step before inserting large-bore Lévy-type spiral drains for irrigation-aspiration. These drains can be removed temporarily to allow complementary local water jet debridement to evacuate necrotic debris [21].

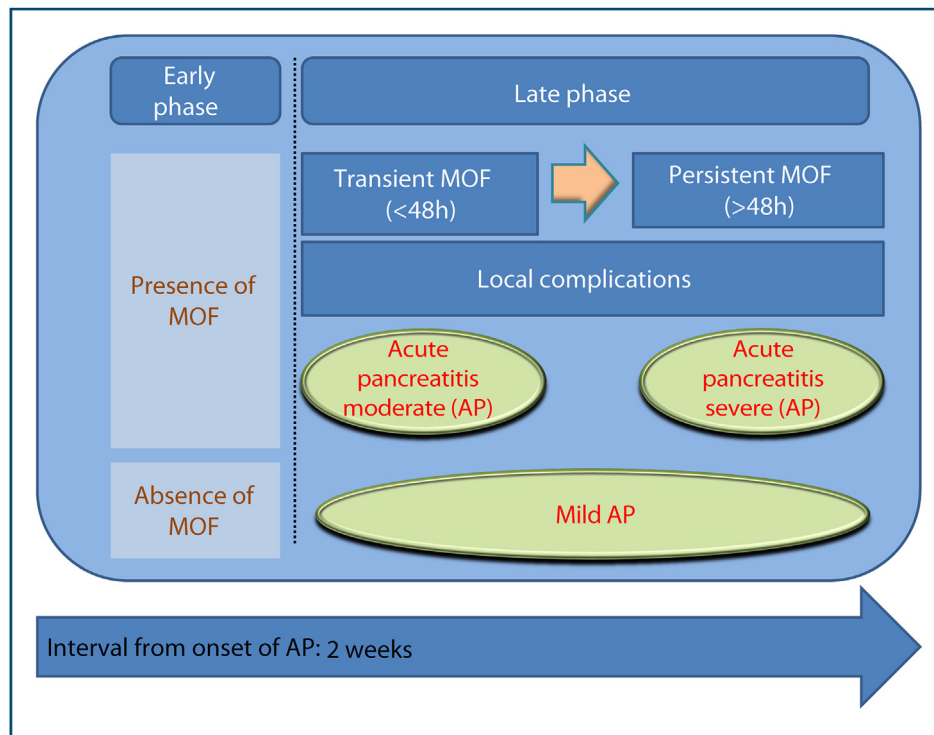


Figure 1. Revised acute pancreatitis classification. DMV: Multi-Organ Failure (MOF); PA = AP: Acute pancreatitis.

Necrosectomy via a direct retroperitoneal approach

The direct retroperitoneal approach is rarely used because of the difficulty of performance through a narrow pathway, but it is the approach of choice for multi-operated patients, with less mortality than the transperitoneal approach, allowing placement of effective dependent drainage; its major disadvantage is that it does not allow exploration of the entire peritoneal cavity [22].

The direct retroperitoneal approach is performed through a lateral sub-costal incision most often on the left with the patient is placed in right lateral decubitus; the incision is 10 to 15 cm long in the prolonged direction of the 12th rib. The Toldt fascia is approached by dissection behind the colon and mesocolon, in front of the kidney leading to the pancreatic bed. The tail and mid-portion of the pancreas and the peripancreatic spaces are then manually explored blindly, easily evacuating the necrotic and purulent tissues with finger dissection. A drain is left in place, allowing subsequent regular lavages. Often several interventions are necessary. If the peritoneum is opened, it should ideally be closed with absorbable sutures.

Berne et al. described a synchronous double approach where anterior celiotomy is combined with posterior drainage; this allows exploration of the peritoneal cavity [23]. However, the procedure is complex and is rarely performed.

Transperitoneal laparoscopy

In 2006, Parekh described a technique for transperitoneal hand-assisted laparoscopic necrosectomy [24]. The patient is positioned in 60° of lateral decubitus on the same side as the collection. The technique calls for two 10–12 mm trocars in the midline and a GelPort® in the right upper quadrant. The approach to the pancreas is infracolic, trans-mesocolic: the greater omentum is displaced superiorly; an incision is made above the duodenojejunal angle of Treitz.

The mesocolon is often attenuated by fluid collected in the lesser sac and can easily be opened with a finger. Once the debridement is finished, suction drainage is placed adjacent to the pancreas. Patients with rigid or thickened greater omentum are not good candidates for laparoscopy because exposure can be difficult. Of the 18 patients evaluated for initial laparoscopic debridement, only four required complementary surgical exploration. Mortality was 11% while morbidity was 58% [24].

However, this technique is not used very often and therefore it is difficult to compare it to other available techniques. One retrospective study comparing the laparoscopic approach to traditional surgery found that the complication rate, and in particular, the postoperative pancreatic fistula rate (RR=0.58, $P=0.006$), blood loss (270 mL vs. 460 mL, $P=0.014$), and mean duration of postoperative stay (35 vs. 43 days, $P=0.031$) were in favor of laparoscopy [25].

Other minimal-access techniques

Radiologic drainage

Radiologic drainage, first described in 1998, is used to obtain bacteriologic samples and to evacuate fluid within the necrotic areas [26]. It can also guide future endoscopic or laparoscopic approaches.

CT scan maps the degree of extension of necrosis, with precisions as to the location, size, potential communications, and structures in contact. Magnetic resonance imaging, with high-resolution contrast enhancement, can be used to better evaluate the nature and thickness of the necrotic extension (macro debris, blood clots, necrotic sludge; liquefied portions), and thus optimize the approach by anticipation of the best modality and probability of successful drainage [27]. Another advantage of MRI is to diagnose superinfection: the diffusion coefficient appears weaker in infected pancreatic liquid collections ($P \leq 0.031$), with a sensitivity and specificity of 67% and 96%, respectively.

The drainage modality should be discussed collegially between endoscopists and surgeons. It is important to avoid any contact between the drain and the gastro-intestinal tract, to avoid contamination of the collection in order to minimize the risk of gastrointestinal fistula. Thus, percutaneous left lumbar retroperitoneal radiologic drainage is often proposed because it allows direct access to collections in the lesser sac and dependent drainage. In the absence of improvement after 72 hours, the drainage should be optimized: adding one or several drains to collections that are inadequately drained [28], increasing the caliber of drains to 30F or using aspiration/lavage for continuous lavage. A literature review collecting 947 patients reported mortality and morbidity rates of 20% and 28%, respectively, with radiological drainage [29].

Videoscopic Assisted Retroperitoneal Debridement (VARD)

VARD is often performed after radiologic drainage and can make use of the same tract [30]. The patient is positioned supine, left side elevated. A 5 cm incision is made either below the 12th rib or in the 11th intercostal space, at the level of the radiologic drainage site. A finger inserted along the drain can break through the fibrous shell. Necrosectomy is then performed with a lung grasper and suction device. A laparoscopic camera adapted to a 0° scope, or a nephroscope (easier to use), is inserted through the incision into the retroperitoneum. Two large bore surgical drains are placed in the collection through the incision and the skin is closed between the two drains.

Possible complications include colonic fistula, hemorrhage, or intraperitoneal contamination by infected debris during hydrodissection when the lesser sac is opened unintentionally.

In a prospective cohort of 639 patients with ANP, the mortality and prevalence of complications were statistically significantly lower after minimal access retroperitoneal necrosectomy vs. traditional necrosectomy (19% vs. 38% and 55% vs. 81%, respectively) [17]. The long-term risk of pancreaticocutaneous fistula was approximately 20%, with a risk of chronic fistula, due to disruption of the main pancreatic duct disruption in communication with the drainage tract [31].

Endoscopic necrosectomy

The risk of chronic pancreaticocutaneous fistula after VARD and the progress made in interventional endoscopy have kindled interest in the transgastric endoscopic approach. As for retroperitoneal necrosectomy after radiologic drainage, the endoscopic approach requires an initial intraluminal transgastric approach. Surgical necrosectomy should be envisioned if the drainage procedure is ineffective [32].

These procedures are usually possible under conscious sedation; echo-endoscopic guidance permits correct visualization of the extension of the necrosis and determination of the optimal site for needle insertion and CO₂ insufflation to limit the risk of gas embolism. The collection is first punctured with the needle, then the contents are aspirated and a "cystogastrostomy" is performed with monopolar current. The gastrotomy orifice is then balloon-dilated to 8 mm to allow the introduction of at least two plastic double pigtail catheters. Certain teams [31] recommend continuous nasocystic lavage of the collection although there is no proof that this is necessary [33,34]. The cyst-gastrostomy is then progressively dilated over several days until reaching 17 mm.

Necrosectomy can then be performed with a simple or basket Dormia catheter, after endoscopic exploration of the lesser sac.

The endoscopic approach can be used to evacuate necrotic material from the lesser sac and, for some authors, the left paracolic gutter: one study reported an efficacy ranging from 80 to 93%, with morbidity ranging from 8 to 33% and mortality between 0 and 8% [35]. Hemorrhage is the main complication. In one German series with a median long-term survival of 44 months, 84% of patients had a prolonged positive outcome; 4% finally required operation for pseudocyst while 13% relapsed [36].

A randomized study by the Dutch Pancreatitis Study Group "PENGUIN" compared endoscopic transgastric necrosectomy to video-assisted retroperitoneal surgical necrosectomy for super-infected ANP [37]. Endoscopic necrosectomy was not associated with multi-organ failure (0% vs. 50%, $P=0.03$), had a lower rate of pancreatic fistula (10% vs. 70%), but mortality was unchanged. However, endoscopic necrosectomy required more procedures than surgery (3 vs. 1; $P=0.007$). These conclusions, however, warrant precaution because of the limited number of patients ($n=20$), substantial differences in CRP levels between the two groups, and an exceptionally high (40%) mortality rate.

Several authors have criticized the endoscopic route because it requires favorable anatomical conditions, iterative procedures and is highly operator-dependent. One systematic review on endoscopic necrosectomy reported a 76% success rate with an average of four sessions for an expert operator [38]. Another Dutch multicenter randomized controlled trial, TENSION, is underway [39]. This trial was set up to compare an "all endoscopic" approach, that is endoscopic trans-luminal drainage, then, if necessary, endoscopic necrosectomy, to the "step-up approach", that is, initial percutaneous drainage followed by video-assisted retroperitoneal surgical necrosectomy.

The results of endoscopic necrosectomy are encouraging and even if the current recommendations remain unclear, endoscopic transgastric necrosectomy warrants consideration whenever local conditions permit (favorable anatomy, skilled and experienced operator) because it is less morbid than the retroperitoneal approach and limits the risk of chronic pancreaticocutaneous fistula.

"Step-up approach"

The morbidity and mortality incurred by surgical treatment as well as increased radiologic and endoscopic therapeutic possibilities were the building blocks leading to the concept of the "Step-up approach". This consists of a step-by-step management plan, based on progressively increasing the invasiveness, when the previous step has failed for at least 72 hours. In this approach, the clinical response is defined by the improvement of two organ failures or at least a 10% improvement of two of three of the following parameters: leukocyte count, temperature or CRP.

The "step-up approach" requires strict multidisciplinary collaboration between radiologists, endoscopists, surgeons and intensivists in order to ensure that everything possible was done at each step to delay the need to proceed to the next step, and to decrease the morbidity of each procedure.

The multicenter study PANTER, published in 2010, is the first randomized trial comparing the "step-up approach" to traditional surgery in 88 patients [40]. The mini-invasive approach consisted of initial left retroperitoneal drainage,

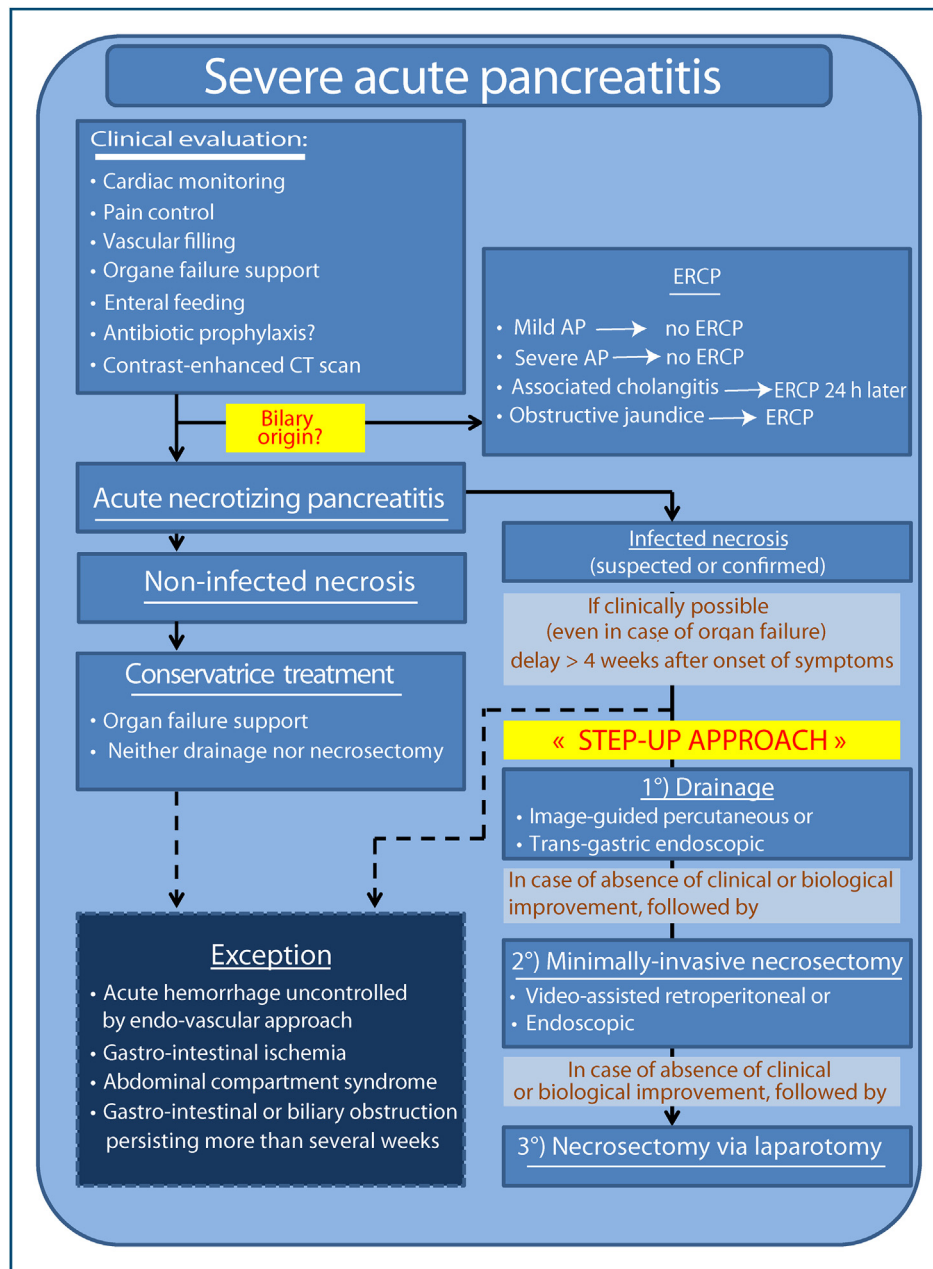


Figure 2. Management algorithm for severe acute pancreatitis. AP: Acute Pancreatitis; CPRE: Endoscopic retrograde cholangio-pancreatography (ERCP).

preferentially by percutaneous interventional radiology or, second-line endoscopy. In case of failure, video-assisted retroperitoneal necrosectomy was performed. If surgery was required, a necrosectomy via bilateral subcostal laparotomy with double drainage and immediate abdominal closure was performed. A composite score associating death and/or major complications (multi-organ failure, perforation, fistula, hemorrhage) was found to be statistically significantly lower in the “step-up approach” group (RR=0.57, $P=0.006$). However, looking at the criteria separately, there was no statistically significant difference found in overall mortality (19 vs. 16%; $P=0.70$), intra-abdominal hemorrhage (RR=0.73, $P=0.48$), enterocutaneous fistula or organ perforations requiring operation (RR=0.63, $P=0.32$). For the authors, the “step-up” strategy led to reduced severe complications by minimizing the surgical trauma in these fragile patients. After evacuation of infected fluids,

necrosis can be left in place if patient status improves as 35% of patients in the “step-up” group were treated exclusively by drainage alone, without necrosectomy. Lastly, patients in the “step-up” group developed pancreatic insufficiency less often (new onset diabetes 16% vs. 38%; $P=0.02$) and had fewer incisional hernias (7% vs. 24%).

Thus, the current strategy for patients with infected ANP is summarized by the “3-D approach”: Delay, Drain and Debride (Fig. 2). The “step-up approach” aims to control the source of infection, without necessarily removing all infected necrotic tissue.

For patients with clinical signs of severity, percutaneous or endoscopic drainage should be preferred for the diagnosis and treatment of super-infected ANP [41,42]. The choice of approach depends on the topographic extent of collections and the experience of the center: drainage can be radiologic or endoscopic, accordingly [43]. If there is no improvement

after drainage, necrosectomy should be performed. The endoscopic or retroperitoneal routes are recommended.

Because of the substantial heterogeneity between different centers in terms of operators and material, it seems best to recommend the technique with which the team feels most comfortable and with which it obtains the best results. Such complex management schemes require expertise, multidisciplinary competencies (surgeon, radiologist, endoscopist) and a versatile technical platform, requiring transferring to specialized centers as necessary.

Emergency surgery for acute complications

Other than the treatment of pancreatic necrosis, other acute complications requiring emergency surgery can arise in ANP and severe AP. The clinical diagnosis of acute complications is most often heralded by sudden onset of circulatory failure. Imaging, particularly contrast-enhanced CT scan, can lead to the etiologic diagnosis and help to guide treatment.

Acute intra-peritoneal bleeding

Hemorrhage is a rare complication of AP, occurring in 1.3% of patients [44]. The most frequent causes of bleeding are: (i) iatrogenic, after an invasive procedure, (ii) erosion of peripancreatic vessels (in particular splenic), by pancreatic juices, giving rise to pseudo-aneurysms that can rupture secondarily, and (iii) splenic and/or portal vein thrombosis that can lead to bleeding esophageal or gastric varices or splenic rupture [45]. The mortality rate of pancreatic-related hemorrhage is 50% [46]. The treatment of choice is selective embolization or insertion of covered stents for arterial causes, but sometimes surgery is necessary in the wake of failed interventional radiology or when severe shock prevents its use [47]. While routine CT scan is not recommended to search for pseudo-aneurysm during APN [43], this investigation is useful for prophylactic endovascular interventional radiology (embolization or covered stent insertion).

Abdominal Compartment Syndrome (ACS)

Extravascular fluid accumulation during ANP can lead to the onset of ACS [48]. Diagnosis is often difficult but should be considered when the Intra-Vesical Pressure (IVP) exceeds 20 cm H₂O in association with renal failure (decreased urine output) or restrictive respiratory insufficiency [49,50]. According to current definitions, ACS has been reported in 27% of patients with ANP [51] and in spite of adapted surveillance and therapy, mortality remains high, ranging from 50 to 75%. This makes intra-abdominal pressure surveillance mandatory in management of severe AP.

The onset of ACS calls for emergency surgical decompression with laparostomy. In a porcine experimental model, statistically significant improvement in hemodynamic, respiratory and renal function occurred when decompression was performed within six hours of onset [52]. In practice, management of ACS in the context of AP is often initially medical (reduced fluid loading, enteral decompression, curarization to increase abdominal wall compliance). Occasionally, percutaneous drainage of fluid collections may be necessary, particularly in patients with IVP > 25 mm Hg associated with new onset organ failure, refractory to medical

treatment plus nasogastric and rectal decompression [43]. In a recent retrospective study [53], mini-invasive percutaneous drainage seems to decrease mortality in patients with ACS and/or early-phase ANP compared with decompressive laparotomy (19% vs. 53% mortality, $P < 0.001$). Complications are also reduced (41% vs. 80%, $P < 0.001$). These results should however be interpreted with caution because the populations were not comparable.

In the literature, outcomes for vacuum-assisted open abdomen are variable, and are biased by the low incidence of ACS in AP, thus leading to confusion between the different levels of severity. One meta-analysis totaling 103 patients reported 49% mortality associated with decompressive laparotomy performed in 74% of cases [54]. The mean decrease in IVP was 15 mmHg. This meta-analysis included only small sample studies with methodological flaws, which did not allow the authors to come to any clear recommendation as to the best timing and method of invasive procedures or to comment on their respective clinical effects.

The goal of the current DECOMPRESS clinical trial (ClinicalTrials.gov NCT00793715) is to compare decompressive laparotomy with temporary abdominal closure to iterative drainages without formal surgery in patients with ACS during severe AP. This study plans to recruit approximately 100 patients divided into two groups in five hospitals.

Ischemia and gastrointestinal perforation

Gastrointestinal necrosis occurs in 10% of ANP [7]. In one autopsy study including 48 patients with ANP, 27% had ischemic enterocolitis [55]. In case of clinical suspicion, contrast-enhanced abdomino-pelvic CT scan should lead to diagnosis showing a lack of enhancement or even perforation of the gastrointestinal wall. Perforations are usually secondary to inflammatory peripancreatic vascular thrombosis by microvascular involvement, enhanced by ACS. The potential for progression of bowel ischemia after initial surgery can justify the principle of a "second look" 24–48 h later [56].

Surgical treatment of ischemia or perforation in AP remains poorly codified. In case of gastrointestinal resection, a stoma is strongly recommended. Exteriorization of the intestinal segments can be difficult when the mesenteries are thickened. When intestinal viability is doubtful, and drainage is in contact with the gastro-intestinal tract, a lateral protective ileostomy can avoid resection. In one series of 30 patients, ileostomy seemed to prevent secondary colonic ischemic complications [57].

Conclusions

Severe AP is associated with high morbidity and mortality. In the era of flourishing mini-invasive strategies allowing delay of open necrosectomy, it is important not to miss the indication for emergency surgery. Outside this situation, surgical abstention during the first month after admission should be the rule, in order to decrease the morbidity and mortality associated with drainage.

In the setting of superinfected necrosis, the "step-up approach" should be used. When the necrosis is organized, parenchyma-sparing procedures seem to decrease mortality compared to early surgery and also decrease the functional consequences. Optimal radiologic or transgastric endoscopic drainage should be the first-line option before attempting any surgical necrosectomy. This can be performed by a

retroperitoneal or endoscopic approach. Necrosectomy via midline or bilateral subcostal laparotomy still has specific indications as a salvage procedure in case of failure of less invasive treatment.

Keypoints

- The indications for emergency surgery are ischemia and gastrointestinal perforation, the abdominal compartment syndrome and failure of non-surgical strategies.
- Infection of necrosis substantially worsens the prognosis in acute necrotizing pancreatitis.
- Necrosectomy should be performed later than four weeks after the onset of symptoms whenever possible.
- Optimally, radiologic or endoscopic drainage should precede any necrosectomy.
- Laparotomy should be chosen only in case of failure of radiologic, endoscopic or mini-invasive surgical drainage, because it increases the morbidity and mortality compared to the other approaches.
- The contemporary therapeutic strategy is summarized in the 3 D's: "Delay, Drain and Debride".

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The authors declare that they have no competing interest.

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