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Review

Necrotizing pancreatitis: A review of the interventions

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ABSTRACT

Acute pancreatitis may have a wide range of severity, from a clinically self-limiting to a quickly fatal course. Necrotizing pancreatitis (NP) is the most dreadful evolution associated to a poor prognosis: mortality is approximately 15% and up to 30–39% in case of infected necrosis, which is the major cause of death.

Intervention is generally required for infected pancreatic necrosis and less commonly in patients with sterile necrosis who are symptomatic (gastric or duodenal outlet or biliary obstruction). Traditionally the most widely used approach to infected necrosis has been open surgical necrosectomy, but it is burdened by high morbidity (34–95%) and mortality (11–39%) rates.

In the last two decades the treatment of NP has significantly evolved from open surgery towards minimally invasive techniques (percutaneous catheter drainage, per-oral endoscopic, laparoscopy and rigid retroperitoneal videoscopy).

The objective of this review is to summarize the current state of the art of the management of NP and to clarify some aspects about its diagnosis and treatment.

1. Introduction

Acute pancreatitis (AP) has increased in incidence reaching up to 0.7 hospitalizations for 1000 inhabitants in the last decade in the US [1]. In about 80% of the patients AP is mild and self-limiting, but in up to 20% it may run a severe course with pancreatic parenchymal and/or peripancreatic tissue necrosis, responsible for substantial morbidity and mortality rate up to 27% [2]. The major cause of death is the infection of the necrotic tissue, which is associated with a poor prognosis: mortality is approximately 15% in patients with necrotizing pancreatitis (NP) and up to 30–39% in those with infected necrosis (which occurs at some point in the clinical course in about a third of patients with necrosis) [3–5].

Intervention is generally required for infected pancreatic necrosis and less commonly in patients with sterile necrosis who are symptomatic (especially in case of gastric or duodenal outlet or biliary obstruction). The traditional treatment so far has been open surgical necrosectomy: it provides a wide access to infected necrosis, but it is highly invasive and associated with reported morbidity rates of 34–95% and mortality rate of 11–39%, due to the physiologic stress of the laparotomic debridment [6–9]. During the last two decades the treatment of NP has evolved towards less invasive techniques: laparoscopy, retroperitoneal and per-oral endoscopic approach and percutaneous image-guided drainage. These minimally invasive techniques may be nowadays either an effective alternative or a complementary approach to open surgery. They may allow to postpone surgery in order to optimize the timing of necrosectomy or even to avoid it.

Abbreviations: AP, Acute Pancreatitis; NP, Necrotizing Pancreatitis; MAP, Mild Acute Pancreatitis; MSAP, Moderately Severe Acute Pancreatitis; SAP, Acute Pancreatitis; IEP, Interstitial Edematous Pancreatitis; APFC, Acute Peripancreatic Fluid Collection; PP, Pancreatic Pseudocyst; ANC, Acute Necrotic Collection; WON, Walled-Off Necrosis; CECT, Contrast-enhanced Computed Tomography; MRI, Magnetic Resonance Imaging; EUS, Endoscopic Ultrasonography; ERCP, Endoscopic Retrograde Cholangiopancreatography; FNA, Fine Needle Aspiration; PCD, Percutaneous Catheter Drainage.

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There is a huge variation in conceptual and technical approaches to interventions for NP, and the evidence of the efficacy of them risks to be unclear. This work aimed at describing all the available treatments for NP by reviewing their last reports.

2. Classification of acute pancreatitis

The Atlanta classification of AP of 1992 was revised in 2012. The AP is distinguished as follows: mild acute pancreatitis (MAP), defined as pancreatitis without organ failure (such as renal or pulmonary failure), or complications (such as necrosis or pseudocysts); moderately severe acute pancreatitis (MSAP), defined by organ failure lasting <48 h, or by local complications; severe acute pancreatitis (SAP), reserved for cases in which organ failure lasts >48 h [10].

Interstitial edematous pancreatitis (IEP) is defined by the lack of pancreatic or peripancreatic necrosis on imaging, and is distinguished from necrotizing pancreatitis (NP), which is subdivided into 3 categories: parenchymal necrosis, peripancreatic necrosis or combined necrosis: all of them may be infected or sterile.

In the setting of AP, typically IEP, a peripancreatic fluid collection occurring within the first 4 weeks is define as an acute peripancreatic fluid collection (APFC) and is characterized by the lack of both a well-defined wall and pancreatic or peripancreatic necrosis on imaging. When an APFC persists over 4 weeks, a well-defined wall will develop and the term pancreatic pseudocyst (PP) is applied.

In the setting of NP, a collection of not only fluid but also necrosis involving the pancreatic parenchyma or the peripancreatic tissues is defined as acute necrotic collection (ANC) when seen within the first 4 weeks of the disease. Like APFCs, ANCs lack a well-defined wall. When an ANC persists over 4 weeks and becomes encapsulated, it is defined as walled-off necrosis (WON). In summary, APFC contains no necrotic material, whereas ANC contains fluid and necrosis; when these two entities persist over 4 weeks, they become PP and WON, respectively [10].

3. Complications of necrotizing pancreatitis

3.1. Infection

About one third of patients with pancreatic necrosis will develop infection, which is associated with markedly increased morbidity and mortality [3]. Peak occurrence is between 2 and 4 weeks after presentation, but it may occur at any time during the clinical course of NP. Gram-negative bacteria are the usual responsible but a trend towards increasing infections with Gram-positive and multiresistant organisms has been observed [11,12]. The development of infection should be suspected in case of new-onset fever, tachycardia and increasing leukocytosis and it may lead to sepsis, systemic inflammatory response syndrome (SIRS) or organ failure (typically later in the course of disease) [3,13]. The distinction of sterile from infected necrosis is difficult but it is very important as it greatly affects the patient's prognosis and management. The presence of gas (resulting from gas-forming organisms or from a fistula to the stomach, small bowel, or colon) on imaging studies is highly suggestive of infection but it is only present in a minority of cases. However, the gas does not need to be present to state that there is an infection [14,15]. Prophylactic antibiotic use in the presence of AP has not proved to decrease the incidence of infection or mortality and it is not recommended as prophylaxis, as shown in the meta-analysis by Wittau [16]. However, the Cochrane review by Villatoro showed that antibiotic prophylaxis was associated with significantly decreased mortality but not infected pancreatic necrosis in patients with NP: beta lactams were associated with significantly decreased mortality and infected pancreatic necrosis, but quinolone plus imidazole regimens were not [17].

3.2. Bleeding

Hemorrhage can develop in patients with NP especially in the late phase; it is estimated to occur in 1%–6.2% of patients with AP [18,19]. The bleeding may occur within the gastrointestinal tract, the peritoneal cavity, fluid collections or in the pancreatic parenchyma. It usually results from enzymatic degradation of local vessels in the peripancreatic tissues and the development of pseudoaneurysm [20]. Bleeding will often manifest as sudden deterioration in hemodynamics with drop in hemoglobin, the development of a new mass or bloody output from drains placed in the pancreatic bed. Angiography with embolization should be considered as the initial line of therapy and surgery should be reserved for refractory cases [21]. Another cause of gastrointestinal bleeding in pancreatitis is variceal bleeding associated with splenic vein thrombosis, which itself results from pancreatitis and leads to left-sided portal hypertension. Bleeding occurs in 4%–12.6% of patients and splenectomy is rarely recommended [22].

3.3. Abdominal compartment syndrome

The development of abdominal compartment syndrome is associated with a mortality of 49% and a morbidity ranging from 17% to 90% [23]. Surgical decompression has been employed in the form of standard midline laparotomy, bilateral subcostal peritoneum-sparing laparotomy, and subcutaneous, skin-sparing, linea alba fasciotomy [24,25]. In a retrospective study Mentula reported that early abdominal decompression is associated with improved renal and respiratory function and reduced mortality [26]. However, the recent systematic review by van Brunschot suggested that strong data are still lacking regarding the management of abdominal compartment syndrome in the setting of AP [23].

3.4. Pancreatic duct disruption and stricture formation

The necrosis of a long, central part of the pancreas with preservation of viable tissue in the tail may be a consequence of NP. This isolated remnant is in discontinuity with the gastrointestinal tract because the pancreatic duct has been disrupted, resulting in the formation of a pancreatic or peripancreatic collection, pancreatic ascites, pancreatic effusion or pancreatic fistula [27].

Non-operative management of pancreatic duct disruption is often possible and is best performed with a multidisciplinary approach, such as what has recently been termed the SEALANTS multidisciplinary approach (Somatostatin, External drainage, ALternative nutrition, Antacids, Nil-per-os, Total parenteral nutrition, and a Stent in the pancreatic duct) [28]. Surgery with pancreatectomy or internal drainage of the cyst can be reserved for patients who fail non-operative therapy [29,30].

Pancreatic-duct strictures can develop after an episode of NP and may later result in fibrosis and scaring, which is associated with recurrent pancreatitis [31].

4. Diagnosis

4.1. Computed tomography (CT)

Contrast-enhanced Computed Tomography (CECT) is the standard imaging modality in the setting of AP. Because the revision of the Atlanta classification relies so heavily on morphologic criteria to

define the various sequelae of AP, CECT with both early arterial phase and portovenous phase (ideally using bolus-tracking to avoid miss-timings related to cardiac output) is essential for it [32,33]. Although CT is not routinely required on presentation of AP, unless necessary to rule out other pathology, because it does not predict the severity of AP better than other commonly used systems based on clinical and biochemical parameters. Rather, it is often used on presentation due to its wide availability and high degree of accuracy [34]. The most important role for CECT is the diagnosis of pancreatic parenchymal necrosis, determining the extent of necrosis and diagnosing local complications as venous thrombosis and pseudoaneurysms [9]. The ideal time for assessing the sequelae of acute pancreatitis with CECT is after 72 h from the onset of symptoms since a complete pancreatic necrosis may not occur in some patients until up to 5 days, edematous or transiently ischemic parenchyma masquerading as necrosis may resolve on subsequent imaging and local complications not initially present can subsequently develop without clear clinical correlates [35,36]. Repeat CT imaging is also suggested when the clinical presentation significantly changes, as it may happen with fevers, decrease in hematocrit, or sepsis. Moreover, CT is of course an indispensable adjunct to guide needle and catheter placement and is used to assess success of treatment in patients having undergone percutaneous, endoscopic or operative interventions. Disadvantages of CECT are radiation exposure, potential nephrotoxicity associated with intravenous contrast media and the difficulty to detect underlying necrotic debris in an acute necrotic collection or WON, especially fluid-predominant collections [34].

4.2. Magnetic resonance imaging (MRI)

MRI may be equivalent to CT for the detection of parenchymal necrosis [34,37,38]. MRI and MRI cholangiopancreatography are often reserved to detect choledocholithiasis not visualized on CECT images and to delineate pancreatic ductal anatomy. Moreover, MRI is superior in detecting non-liquid material in pancreatic and peripancreatic collections and disconnected pancreatic duct in the subacute phase [29]. In patients with very poor renal function, who can therefore receive neither MRI nor CT contrast agents (typically with GFR <35 mL/min), non-contrast-enhanced MRI (fat-suppressed T1-weighted images) provides better resolution and structure definition than non-contrast-enhanced CT. Arvanitakis compared CT and MRI in the detection of areas of hypoperfusion compatible with pancreatic necrosis, thus finding MRI to have a higher sensitivity (83% vs 78%) and specificity (91% vs 86%) [37]. Although CECT is still the workhorse of imaging for NP in most institutions, some groups prefer MRI [38]. Other advantages of MRI include its lack of ionizing radiation, which is especially useful for those patients who are pregnant or need serial, surveillance imaging [36]. However, MRI cannot be performed in the presence of a pacemaker or other metallic objects and it is more prone to motion artifact and many patients with NP are unable to breath-hold adequately.

4.3. Endoscopic ultrasonography (EUS)

EUS seems to be superior to CT to detect non-liquid necrosis and debris within pancreatic and peripancreatic collections [9,34]. EUS has the advantage of providing the highest available sensitivity in detecting bile duct stones without the risk associated with endoscopic retrograde cholangiopancreatography (ERCP) and it can be done by the bedside in severely ill patients [9,38]. Moreover, EUS allows the combination of imaging with image-guided intervention. Limitations are the tendency to overestimate the necrotic debris content of pancreatic fluid collections and the availability of skilled endosonographers [9].

4.4. Fine needle aspiration (FNA)

Image-guided FNA was introduced more than 20 years ago to obtain a culture of the pancreatic collection. In the past, a positive aspirate was thought to mandate immediate surgical intervention [39]. Trends in therapy have modified this approach insofar that the clinical relevance of FNA has been diminished: early interventions are avoided as much as possible, minimally invasive percutaneous or endoscopic interventions are preferred early in the course of the disease (to avoid or postpone surgery). Therefore, the culture may be obtained at the time of intervention and the simple diagnostic FNA is not necessary. Moreover, infected necrosis can be managed with antibiotics and supportive cares until the necrotic collection partially liquefies and walls-off, thus allowing safer organ-preserving interventions [3]. Nowadays, there are relatively few indications for purely diagnostic FNA as suspicion of fungal superinfection when combinated antibiotic therapy does not normalize the clinical and laboratory parameters in patients with assumed infected necrosis [9].

5. Treatments for infected necrosis

5.1. When to intervene?

The main question in the management of sterile and infected pancreatic and peripancreatic necrosis is if and when the intervention is required.

A sterile acute necrotic collection does not almost ever require intervention in the early course of disease, and in the later phase it requires intervention only in the presence of symptoms (such as abdominal pain or mechanical obstruction) [40].

An infected acute necrotic collection may occasionally require early intervention. Radiological or endoscopic drainage should be preferred in order to avoid or postpone surgical debridment, due to its high morbidity and mortality [40].

When an infected necrosis is walled-off and demarcated, with at least partial liquefaction and discrete encapsulation (typically after 4–6 weeks from the onset of the disease), the intervention is mandatory in any procedure [40].

An asymptomatic WON does not require intervention regardless of its size and extension, because it may resolve spontaneously over time, even if it may rarely become infected [40].

A symptomatic WON generally requires intervention late in the course of the disease (>4 weeks) in case of infection, pain, or obstruction of a viscus or bile duct [40].

The intervention within the first few weeks of the onset of AP is required when an infected acute necrotic collection is diagnosed and associated with clinical deterioration and signs of sepsis. Otherwise, clinical deterioration despite maximum medical support (including intensive care and specific organ support) does not seem to be an indication for local treatment (such as radiological, endoscopic, or surgical drainage or necrosectomy) [41,42]. These patients may undergo surgery with the first weeks of onset of AP as a last chance even if the process is sterile, but the prognosis is poor regardless of the intervention [40,41]. Only in abdominal compartment syndrome the early surgical or percutaneous decompression may be life-saving [40].

In patients with infected necrosis, delayed intervention is superior to early intervention. The debridment of pancreatic necrosis before 3 weeks increases the risk of bleeding and other adverse events. The delay of the intervention allows the demarcation of necrotic from vital tissue, so that if necrosectomy is performed later the resection of vital tissue is minimized, thus leading to better

long-term endocrine and exocrine function and a reduction in post-operative adverse events [41,43,44]. Moreover, the use of less invasive techniques allows to postpone or to avoid the surgical debridment, thus improving the outcome.

The guidelines by the International Association of Pancreatology in 2002 advocated that the delay in open surgery for at least 3–4 weeks led to lower morbidity and mortality rates than earlier intervention [45]. In a RCT Mier showed that early necrosectomy (within 2–3 days after the onset of AP) increased morbidity and mortality if compared to delayed intervention (after at least 12 days) [44]. The study by van Santvoort (Dutch Pancreatitis Study Group) demonstrated that early surgery was an independent predictor of poor outcome in patients with acute NP [46]. The series by Reddy, Wittau, Papachristou and Olah, in which timing of intervention was changed within a single institution, confirmed the advantage of delayed surgery [42,47–49].

In the last decade, primary non-interventional medical treatment with administration of antibiotics alone has been proposed for infected necrosis. The recent series by Olah, Runzi, Sivasankar, Garg and Wysocki confirmed that clinically stable and minimally symptomatic patients can be treated using antibiotic therapy without any intervention [49–53]. The intervention is required in case of clinical deterioration.

5.2. How to intervene?

The interventions to drain and/or debride pancreatic and peripancreatic necrosis are distinguished between open surgical (laparotomic transperitoneal or flank incision retroperitoneal approach) and minimally invasive (percutaneous, laparoscopic, retroperitoneal, endoscopic transmural or combined approach).

5.3. Open surgical debridment

Since in 1886 Senn claimed that removing necrotic pancreatic and peripancreatic tissue would be beneficial for patients with severe AP, and in 1925 Fitz suggested that the sooner the operation was carried out the better for patients with AP, the surgical approach became the standard approach to severe AP [54]. The rationale of AP surgery evolved from exploratory laparotomy to total pancreasectomy in severe AP in the late 1960s and 1970s, to early immediate surgical intervention when the pancreas was proved to be infected in the 1980s, moving to the notion of 100% mortality if AP was treated non-operatively in 1993, to the present concept that patients with severe NP complicated with infection benefit from delayed necrosectomy and drainage expressed in 2007 [3,55].

The open surgical debridment has been the standard treatment for infected necrosis and for symptomatic sterile WON. The oldest and most established approach is open laparotomy and retroperitoneal flank incision with manual debridment. Necrosectomy is performed preserving the structures by blunt dissection. Formal resections are avoided to minimize the incidence of bleeding, fistulae and removal of vital tissue. After necrosectomy, the abdomen can be left open, packed, and repeatedly debrided until there is no residual necrosis. Two other techniques may be adopted for the abdominal closure: “close packing” (the abdomen is closed with packing and external drain remnants, thus allowing repeated open necrosectomy) and “post-operative continuous lavage” (the abdomen is closed and the lavage is performed by irrigation by multiple catheters placed in the lesser sac, in the retroperitoneum and behind the colon) [40]. The review by Werner described a decrease of reinterventions, repeated laparotomies and post-operative morbidity with this approach [56]. The “close packing” was described by Fernandez del Castillo in 1998: it showed that the debridement of pancreatic necrosis followed by closed packing and drainage was accomplished with a low mortality rate and reduced rates of complications and second surgical procedures; these data were confirmed in a largest series in 2008 [57,58]. However, there are still limited data to support the claim that the “close packing” and “post-operative continuous lavage” are superior to planned relaparotomies and open packing [40].

Open necrosectomy is associated with relatively high morbidity (34%–95%) and mortality (6%–25%), according to the series and to the severity of illness at the time of surgery [48,56,58–64]. Potential immediate post-operative adverse events are organ failure, perforation of a viscus, hemorrhage and wound infection, any of which may require reoperation. Long-term complications include chronic pancreaticocutaneous and enterocutaneous fistulae, endocrine and/or exocrine pancreatic insufficiency and abdominal wall hernias. Relaparotomy increases local and systemic trauma and has negative systemic effects on hemodynamics and systemic inflammatory response. Morbidity seems to be decreased by avoiding surgical reinterventions, while mortality is similar (15%–20%) [40]. In 1997 the RCT by Mier showed that delayed surgical necrosectomy is superior to early necrosectomy in terms of morbidity and mortality [44]. In 2010 van Santvoort demonstrated that a step-up approach (with initial percutaneous drainage followed by minimally invasive debridment) was superior to open necrosectomy with post-operative lavage in terms of short-term and long-term morbidity [61].

The benefits of the anterior open approach are the possibility to reach every peritoneal and retroperitoneal sites, to perform cholecystectomy, to treat simultaneous biliary gallstone, to perform feeding jejunostomy. However, cholecystectomy can be usually delayed, bile duct lithiasis can be treated endoscopically, and feeding tube can be placed through the nose or the gastric wall.

5.4. Minimally invasive approaches

So many different techniques for the minimally invasive treatment of pancreatic and peripancreatic necrosis can be classified according to the access route (transperitoneal, retroperitoneal, per-oral transmural, per-oral transpapillary, percutaneous), the method used for visualization (laparoscopic, rigid endoscopic, flexible endoscopic, radiologic, hybrid), and the purpose (drainage lavage, fragmentation, debridment, excision).

5.5. Laparoscopic approach

Laparoscopy almost allows the visualization and the access to all compartments of the abdomen. The pancreatic necrosectomy may be performed with laparoscopic devices or with hand-assisted technique. In most patients a single session debridment of necrotic collection or WON is feasible, while reoperations are needed in 11% and 38% according to Parekh and Gagner respectively [65,66]. Morbidity after laparoscopic necrosectomy was described to be about 21%, mortality 10–18% [65–69]. Potential advantages are less wound infections and pulmonary events than open approach, while risks are uncontrollable bleeding and the dissemination of retroperitoneal infection into the peritoneum.

The retrospective study by Tan was the first comparison between laparoscopic and open surgical treatment of infected pancreatic necrosis. It showed that the complications rate, the estimated blood loss, and the mean post-operative hospital stay was significantly greater in the open group; although the mean operative time was significantly longer in laparoscopy [70]. The recent series by Mathew confirmed that laparoscopic necrosectomy is a promising and safe approach with all the benefits of minimally invasive surgery and a reduced incidence of major complications

and mortality, if compared to open surgery [71].

Laparoscopic enteric drainage involves a peritoneal approach with the creation of a large anastomosis between the stomach or the small bowel and the WON. A single intervention is usually adequate, but this operation is mainly recommended for highly experienced minimally invasive surgeons and well-demarcated WON near the stomach or the small bowel [72].

5.6. Retroperitoneal approach

Minimally invasive retroperitoneal approach is carried out by initially establishing a percutaneous tract into the necrotic collection, usually under radiological guide. Then the tract is enlarged via dilation or with a limited incision to allow the passage of a rigid or flexible endoscope or a laparoscope. Afterwards necrosectomy and lavage are performed.

In the series by van Santvoort, Raraty, Bakker, Connor, Gambiez, Carter, Castellanos and Horvath the average number of intervention was fewer than 3, the periprocedural adverse events of retroperitoneoscopy were less than 5%, the morbidity ranged 10–20%, and the mortality ranged 0–20% (only Bakker and Castellanos reported 27% and 40% respectively) [61,63,64,73–77]. In the large series of 400 patients, Carter reported that this technique reduced the post-operative organ failure and the need of intensive cares, although with an increase in hospital stay, if compared to open surgery [78]. Moreover, the need for open necrosectomy was considerably reduced (from over 90% to less than 10%).

5.7. Percutaneous approach

Image-guided percutaneous catheter drainage (PCD) may be used both as primary therapy and as an adjunct to other techniques (even as salvage management of residual infected collections) [40]. The approach may be transperitoneal or retroperitoneal: the latter is preferred because it avoids peritoneal contamination and enteric leaks and facilitates a step-up approach [61,79]. The diameter of the catheters ranges from 12 Fr to 30 Fr; they are irrigated, manipulated and replaced according to the evolution of the collections. PCD is the most useful for collections that do not resolve, to control sepsis, and as first step (in the step-up approach) before endoscopic debridment or surgery (bridge to surgery) and to drain residual collection after invasive treatments [40].

The systematic review by van Baal in 2011 showed that PCD as primary treatment for pancreatic necrosis was successful in 55.7% of patients (thus not requiring any surgical necrosectomy), with a mortality of 15.4% in case of infected necrosis [80]. The RCT by the Dutch Pancreatitis Study Group reported a success of PCD in 35% of patients [61]. Adverse events as external fistulae occurred in up to 27% [61,81]. However, optimal size, number of drains, and management of them are still not established and depend on each single experience.

5.8. Endoscopic approach

Per-oral flexible endoscopic drainage of pancreatic pseudocyst performed through the papilla or the stomach wall was first described by Gebhardt in 1985 [82]. The irrigation of the WON by a nasocystic catheter passed through a transmural entry was described in 1996 by Baron [83]. The first transluminal direct endoscopic necrosectomy of a WON was first reported by Seifert in 2000 [84,85]. Endoscopic necrosectomy is performed by passing a flexible endoscope transorally and then transmurally into the necrotic cavity. The site of transmural puncture can be visually determined by a bulge (representing the extrinsic compression of the collection into the lumen) in 50–60% of patients [40]. If the bulge is not visible (small collections, low serum albumin, collections located near the pancreatic tail) EUS is used to visualize the collection, to assess its content and to guide the puncture, therefore minimizing the damaging of the adjacent structures. The RCT by Varadarajulu and Park showed that the EUS guide increases the technical success (>95% vs 33–66%) and decreases the adverse events (0–4% vs 13–15%) of endoscopic transmural drainage [86,87].

After the puncture of the stomach or duodenal wall into the cystic cavity, the tract is dilated by a balloon and multiple large-bore double-pigtails stents or removable self-expanding stents are placed. Debridment and lavage are carried out by a variety of devices (baskets, balloons, forceps, nets and irrigation) and 3–6 sessions are necessary to reach the complete debridment.

The outcomes of endoscopic necrosectomy are encouraging. The systematic review of 10 series of endoscopic necrosectomy by Haghshenasskashani showed a complete resolution of the collections in 76% of patients, with overall morbidity of 27% and mortality of 5%, although patients' characteristics differed among the included studies [88]. The RCT by Bakker and the Dutch Pancreatitis Study Group recently reported the superiority of endoscopic necrosectomy over open surgical necrosectomy, with less new-onset of organ failure (0% vs 50%), fewer pancreatic fistulas (10% vs 70%), and lower post-procedural levels of IL-6 ($p = 0.03$) [64]. The retrospective series by Tan recently confirmed that endoscopic necrosectomy had lower complications rate and hospital stay if compared to surgical necrosectomy [89].

The best advantages of endoscopic necrosectomy are the possibility of internal drainage avoiding surgical procedures (with not negligible complications) and external drainage (with possible fistulae). The limitations of endoscopic approach are the need for multiple repeated procedures (under sedation or anehstesia), the quantification of necrotic burden, how to manage a large burden of necrotic tissue, how to manage deep retroperitoneal extension, and the diffulty/impossibility to treat the distal left-sided collections [40]. Moreover, this approach has technical limits as the lack of dedicated instruments, the difficulty to fix the bowel lumen to the cavity wall with staples or sutures, the difficulty to avoid vital structures (as vessels) within the necrotic cavity [40]. Indeed endoscopic necrosectomy needs advanced endoscopic expertise in both ERCP and EUS. There is consensus in considering endoscopic necrosectomy a safe and effective procedure with acceptable morbidity and mortality (lower than open surgery) when performed in specialized centers. However, an aspect must still be clarified: whether complete necrosectomy, or initial endoscopic transmural drainage followed by further endoscopic necrosectomy, or initial percutaneous drainage followed by necrosectomy are superior to each other, therefor further well-designed prospective studies and RCTs are needed 40].

5.9. Combined percutaneous and endoscopic approaches

To combine PCD and endoscopic necrosectomy may be an approach which ensures the advantages of minimally invasive operation, thus avoiding the risks of each technique as external fistulae and repetitive endoscopic interventions. The advantages of PCD are widespread availability, transperitoneal and/or retroperitoneal approach to every abdominal site, possibility to place flush, remove and replace multiple catheters; otherwise the main limitation is the development of pancreatico-cutaneous fistulae, which occurs in about 20% of patients, with the risk that some fistulae does not close because of the communication with an upstream disconnected duct [40,90–92]. The advantages of endoscopic approach are internal drainage and avoidance of external fistulae, although the complete necrosectomy requires multiple repeated

procedures under sedation or anesthesia. The combined approach allows the irrigation of the WON through the percutaneous catheters with egress through the transmural orifice, resulting in a form of debridment. After the resolution of the collection the percutaneous catheters are removed and the transmural stents can remain in place, even indefinitely in case of disconnected duct [40]. However, the endoscopic-percutaneous approach has the same limitations of the endoscopic approach, mainly the location of the WON, that must be placed within 2 cm from the gastric or duodenal wall.

The experience by Ross recently showed that this combined approach resulted in favorable clinical outcomes with complete avoidance of pancreatico-cutaneous fistulae, surgical necrosectomy and considerabler procedure-related adverse events, with disease-related mortality of 3.4% [93]. The previous case-series by the same group reported that the combined approach increased the rate of non-surgical resolution and decreased hospitalization, time to drain removal, number of CT scans and number of placed drains, compared to PCD alone [94].

5.10. "Step-up" approach

The "step-up" approach consists of a first minimally invasive treatment of pancreatic collection followed by a gradually more invasive procedure if the previous fails. The objective is to treat the necrotic collection with as less stress as possible. The first step is usually PCD (preferably into the retroperitoneum via the left flank or through the peritoneal cavity) or endoscopic transluminal necrosectomy. If the drainage fails to control sepsis the next step is per-oral access, if it fails the following steps are the debridment by retroperitoneal endoscopy, up to laparoscopic or open surgery.

The Dutch PANTER trial randomized patients with pancreatic or peripancreatic necrosis to primary open surgery and continuous post-operative lavage or to the "step-up" approach with percutaneous or endoscopic drainage and, if no clinical improvement was seen after 72 h, a second drainage was performed, followed by video-assisted retroperitoneal debridment. Outcomes were significantly better in the "step-up" group compared to open surgery group: considerable morbidity was 40% vs 69%, new onset of organ failure was 12% vs 42%, incisional hernias were 7% vs 24%, new-onset diabetes was 16% vs 38%, respectively. Moreover, 35% of patients in the "step-up" group did not require necrosectomy; however mortality was similar in both groups (19% vs 16%) [95]. Yet, the matched cohort study by Kumar has recently reported that direct endoscopic necrosectomy may be superior to step-up approach for WON with suspected or established infection (because primary PCD generally delayed definitive therapy); thus, given its higher efficacy, shorter length of stay, and lower health care utilization, endoscopic necrosectomy could be the first-line therapy for WON, with primary PCD for inaccessible or immature collections [96].

6. Discussion

Traditionally the most widely used approach to infected necrosis has been open surgical necrosectomy, but in the last two decades the treatment of NP has significantly evolved from open surgery towards minimally invasive techniques (PCD, per-oral endoscopy, laparoscopy, and rigid retroperitoneal videoscopy).

There is a wide variation in conceptual and technical approaches to interventions for NP, and the different minimally invasive techniques are in distinct stages of evolution. Approaches may be combined in selected patients and in extensive peripancreatic collections. The minimally invasive or open surgical approach is often determined by institutional preferences, availability of equipment, expertise, subspecialty background and interest of involved physicians. Care of patients with NP should ideally include a team of specialists in gastroenterological medical management, intensive care medicine, diagnostic and interventional radiology, interventional endoscopy and surgery. However, there is such wide variation in clinical practice that a few physicians with variable expertise are often responsible for managing these patients.

Intervention is required in patients with infected pancreatic and/or peripancreatic necrosis, in patients with clinical deterioration despite medical support and suspected infection, in symptomatic patients (especially in case of obstruction of a viscus), and in patients with sepsis in the absence of another explanation [40]. Urgent intervention is required in case of abdominal compartment syndrome or bowel perforation, but without necrosectomy. Intervention within the first few weeks for NP are generally associated with poor outcomes and should be reserved for infected necrosis in a severely deteriorating patient [40].

Results using various minimally invasive methods are described in this review. Current literature shows that delayed intervention (for at least 3–4 weeks) for NP is superior to early intervention in terms of morbidity and mortality [44]. Moreover, open surgery should be abandoned as first treatment for NP in favour of minimally invasive approaches, because it increases post-operative morbidity, although post-operative mortality does not seem to be influenced [61]. Current evidences favor PCD or endoscopic necrosectomy, even followed by minimally invasive necrosectomy (by videoscopic retroperitoneal or laparoscopic access), as preferred approaches for intervention for infected necrosis [40,61,96]. The "step-up" approach (with first PCD or endoscopic transmural drainage of infected collections, followed by minimally invasive or open necrosectomy) has been shown to be superior to immediate open surgery in terms of short-term and long-term outcomes in patients with infected necrosis [61].

The guidelines of the International Association of Pancreatology (in 2012) recommend endoscopic or percutaneous drainage as the first step in the treatment of NP, followed by surgical necrosectomy only if required, because of ongoing septic status despite targeted antibiotic therapy [97]. However, the best modality of drainage is not specified [97].

It must be highlighted that the reported studies involve heterogeneous patient populations, definitions of infected necrosis, and techniques: as a result, the outcomes are not directly comparable.

7. Conclusion

The surgical treatment of NP has significantly evolved in the last two decades from open surgery towards minimally invasive techniques.

The most important aspects that the current literature show are: delayed intervention (for at least 3–4 weeks) for NP is superior to early intervention in terms of morbidity and mortality, minimally invasive treatments are superior to open surgery in term of short-term and long-term post-operative morbidity, no single approach is optimal for all patients, the best approach is multimodal and adaptable to the individual patient.

The interventions should be chosen in the context of optimal intensive care and medical management and a multidisciplinary approach is required in a center with specialized expertise in interventional radiology, interventional endoscopy, intensive care, nutritional support, and both laparoscopic and open surgery.

Further RCTs and prospective studies, with a consistent number of patients, are necessary to define the corresponding indications of these different techniques of necrosectomy in NP.

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Author contribution

Walter Bugiantella: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Fabio Rondelli: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Marcello Boni: Partecipated substantially in execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting of the manuscript.

Paolo Stella: Partecipated substantially in design, execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting of the manuscript.

Andrea Polistena: Partecipated substantially in the analysis and interpretation of data.

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Nicola Avenia: Partecipated substantially in the interpretation of data; also partecipated substantially in the editing of the manuscript.

Conflict of interests

All the authors declare that they have no conflict of interests.

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