Review

Staged multidisciplinary step-up management for necrotizing pancreatitis

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Background: **Some 15 per cent of all patients with acute pancreatitis develop necrotizing pancreatitis, with potentially significant consequences for both patients and healthcare services.**

Methods: **This review summarizes the latest insights into the surgical and medical management of necrotizing pancreatitis. General management strategies for the treatment of complications are discussed in relation to the stage of the disease.**

Results: **Frequent clinical evaluation of the patient's condition remains paramount in the first 24–72 h of the disease. Liberal goal-directed fluid resuscitation and early enteral nutrition should be provided. Urgent endoscopic retrograde cholangiopancreatography is indicated when cholangitis is suspected, but it is unclear whether this is appropriate in patients with predicted severe biliary pancreatitis without cholangitis. Antibiotic prophylaxis does not prevent infection of necrosis and antibiotics are not indicated as part of initial management. Bacteriologically confirmed infections should receive targeted antibiotics. With the more conservative approach to necrotizing pancreatitis currently advocated, fine-needle aspiration culture of pancreatic or extrapancreatic necrosis will less often lead to a change in management and is therefore indicated less frequently. Optimal treatment of infected necrotizing pancreatitis consists of a staged multidisciplinary 'step-up' approach. The initial step is drainage, either percutaneous or transluminal, followed by surgical or endoscopic transluminal debridement only if needed. Debridement is delayed until the acute necrotic collection has become 'walled-off'.**

Conclusion: **Outcome following necrotizing pancreatitis has improved substantially in recent years as a result of a shift from early surgical debridement to a staged, minimally invasive, multidisciplinary, step-up approach.**

Paper accepted 5 September 2013

Published online 22 November 2013 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9346

Introduction

In recent decades the incidence of acute pancreatitis has increased globally and the burden on worldwide healthcare services is expected to increase even further[1–6]. Some 85 per cent of patients with acute pancreatitis make a quick and uneventful recovery, requiring little more than analgesia with or without minor supportive measures (for example fluid therapy). However, around 15 per cent develop necrosis of the pancreatic parenchyma or extrapancreatic tissue. Failure of one or more organ systems will ensue in approximately 40 per cent of these patients. Only a minority of patients without pancreatic necrosis develop organ failure, but it can sometimes occur[7]. Both complications are independently associated with prolonged hospital admission, and high morbidity and mortality rates. Should pancreatic or extrapancreatic necrosis become infected, mortality rates increase up to 20 per cent[8].

In necrotizing pancreatitis, the type of complication that may develop is closely related to the time from symptom onset, and specific complications may be managed differently at different time points. Therefore, this review addresses staged multidisciplinary 'step-up' strategies

for necrotizing pancreatitis according to time from onset of symptoms. The complications and subsequent management strategies are described for each phase of necrotizing pancreatitis.

Methods

The recommendations in this review are based on the recently revised guidelines[9,10] of the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) and the American Gastroenterological Association. To construct the revised IAP/APA guideline multiple systematic reviews were performed by different groups of experts covering the most important areas of necrotizing pancreatitis. Recommendations for areas of necrotizing pancreatitis that lack solid evidence are based on expert opinion from international experts and consensus within the Dutch Pancreatitis Study Group.

The different events following the time after symptom onset are described in accordance with the most likely chronological presentation to the treating physician. Starting with diagnosis and management on admission, the treatment suggestions for the first week are described, followed by those for weeks 2 and 3, weeks 4–6 and after week 6.

Definition

The 2012 revised classification of acute pancreatitis[11,12] is now considered the new standard for defining acute pancreatitis and its complications (*Table 1*). In the revised classification, mild acute pancreatitis is defined by the absence of organ failure and local complications. Symptoms usually resolve within the first few days after admission and most patients are discharged from hospital within a week. If performed, contrast-enhanced computed tomography (CECT) may reveal interstitial pancreatic oedema occasionally accompanied by extrapancreatic fatty tissue inflammation. Most often the result of gallstones or alcohol abuse, definitive treatment consists of cholecystectomy or alcohol avoidance[1]. Although less common, several types of drug may cause pancreatitis and accordingly changes in medication should be queried on admission[13]. Any possible provoking agent should be discontinued immediately. Acute pancreatitis affects men and women in equal proportions, although alcoholic pancreatitis seems more prevalent in men whereas women are more likely to develop gallstone pancreatitis. The overall mortality rate of acute pancreatitis does not exceed 5 per cent and 75 per cent of patients do not suffer a recurrence[14,15]. In moderately severe acute pancreatitis, patients develop either transient organ failure (lasting less than 48 h) or local complications, such as pancreatic or extrapancreatic necrosis or pancreatic fluid collections. Severe pancreatitis is marked by persisting organ failure (lasting more than 48 h) and is usually accompanied by local complications. The rationale for this cut-off value of 48 h is that organ failure persisting beyond this point is associated with a much higher risk of death[16–19].

Table 1 Overview of the revised classification of acute pancreatitis

Category	Characteristics
Mild	No organ failure No local or systemic complications
Moderate	Organ failure for < 48 h *or* Local* or other systemic† complications
Severe	Organ failure for > 48 h Local or systemic complications usually present

*Such as pancreatic necrosis, extrapancreatic fluid collection, splenic vein thrombosis; †exacerbation of pre-existing co-morbidity, for example chronic lung disease.

Evaluation and diagnosis on admission

Acute pancreatitis is diagnosed when two of the following three criteria are present: pain in the upper abdominal region, raised levels of lipase or amylase at least three times the upper limit of normal, and characteristic findings on cross-sectional abdominal imaging. In most patients the first two criteria suffice for the diagnosis and no imaging is needed. CECT should be carried out only if there is diagnostic uncertainty. The aetiology of pancreatitis should be determined, because it has implications for both short- and long-term management[20].

Laboratory testing

On admission, the serum level of amylase or lipase is merely diagnostic and is not associated with an increased risk of developing complications[21]. Both parameters reach their peak and decrease back to normal in 2–4 days (amylase) and 8–14 days (lipase)[22]. Repeated measurements after admission are not indicated. Increased alanine aminotransferase levels on admission of over 60 units/l show a high probability of a biliary aetiology (positive predictive value 80–90 per cent)[23,24]. Additional blood tests on admission should be carried out to rule out less common aetiologies such as hypertriglyceridaemia and hypercalcaemia.

Table 2 Radiological accuracy for determining biliary origin

	Sensitivity	Specificity	Positive predictive value	Overall
Cholecystolithiasis				
Ultrasonography	High	Moderate	Excellent	High
Choledocholithiasis				
Ultrasonography	Poor	High	Moderate	Moderate
EUS	Excellent	Excellent	Excellent	Excellent
MRCP	Excellent	Excellent	High	Excellent
CECT	High	High	High	High

Poor, below 60 per cent; moderate, 60–74 per cent; high, 75–90 per cent; excellent, 91–100 per cent. EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; CECT, contrast-enhanced computed tomography.

Radiology

Ultrasonography is indicated in all patients with suspected gallstone disease. It is useful for diagnosing cholecystolithiasis, but less accurate for detecting common bile duct stones (*Table 2*)[24–26]. However, significant dilatation of the common bile duct (diameter over 8 mm in patients aged 75 years or less, and more than 10 mm in patients over 75 years of age) is considered positive for a biliary aetiology. Both magnetic resonance cholangiopancreatography and endoscopic ultrasonography have excellent accuracy for detecting choledocholithiasis. Endoscopic ultrasonography is superior in detecting sludge and small stones, especially in non-dilated bile ducts[24,27–29]. Early CECT or magnetic resonance imaging (MRI) might be used to confirm the diagnosis of acute pancreatitis in those rare instances when the diagnosis cannot be established by clinical signs and biochemical parameters, for example if there are clinical signs of an acute abdomen.

Severity prediction

Several predictive scoring systems have been proposed for identification of patients at risk of developing organ failure or pancreatic complications[30–33]. Identification of these patients is important for institution of early supportive measures and for inclusion in clinical trials. Unfortunately, because the discriminatory power of most traditional scoring systems is moderate at best, their clinical applicability is limited[34–36]. More recent endeavours have aimed at identifying single serum markers to predict severity as opposed to the older, more complex, systems that use multiple clinical and biochemical features (such as the modified Glasgow score, Ranson score and the Acute Physiology And Chronic Health Evaluation (APACHE) II)[37]. For example, serum creatinine concentration correlates strongly with the development of pancreatic necrosis, with a positive predictive value of 93 per cent, if blood levels rise to above 1·8 mg/dl (or 159 μmol/l) within 48 h of admission[38]. Blood urea nitrogen levels are a strong predictor of death[32]. A blood urea nitrogen level of 20 mg/l (7·14 μmol/l) or higher on admission, or any rise within 24 h after admission, is associated with an odds ratio for death of 4·6 and 4·3 respectively.

In the first 72 h after symptom onset, necrosis of the pancreatic parenchyma cannot be assessed reliably on CECT[34]. Consequently, CECT has no role in assessing or predicting the severity of disease on admission in the first few days after admission[30,34,39–43].

Management during the first week

Management of necrotizing pancreatitis during the first week of admission consists mainly of frequent clinical evaluation, analgesia and supportive measures (*Fig. 1*). In the first few days after admission, patients should be evaluated for the presence of the systemic inflammatory response syndrome (SIRS). Patients with persisting SIRS have a significantly worse outcome[18,44,45]. Monitoring SIRS is an effective bedside tool for assessment of disease progression because measurement of its components can be repeated easily[9].

In the event of deterioration or absence of clinical improvement at the end of the first week, CECT or MRI is indicated to assess the presence and extent of pancreatic or extrapancreatic necrosis, or extrapancreatic fluid collections[46,47]. Clinical deterioration during the first week is caused most often by progression of SIRS and seldom because of early infection of pancreatic necrosis[48]. As such, surgical intervention is not indicated during this phase unless an ischaemic or perforated viscus is the cause. If emergency surgery is deemed necessary, it is associated with mortality rates of 40–78 per cent[7,49,50]. Early emergency surgery potentially aggravates multiple organ failure, as shown by an increase in APACHE II scores after operation[51,52]. Additionally, complications (such as bleeding, intestinal fistula) are more prone to occur if surgery is performed before the acute necrotic collection has had time to progress to 'walled-off' necrosis (*Fig. 2*). Although there is no compelling evidence to support either of these arguments, the unfavourable outcomes following early debridement have driven clinicians towards more conservative policies in the early phase of the disease[7,50,53–55].

Fluid resuscitation

Fluid resuscitation aims at counteracting the effects of hypovolaemia due to 'third spacing', and is directed at

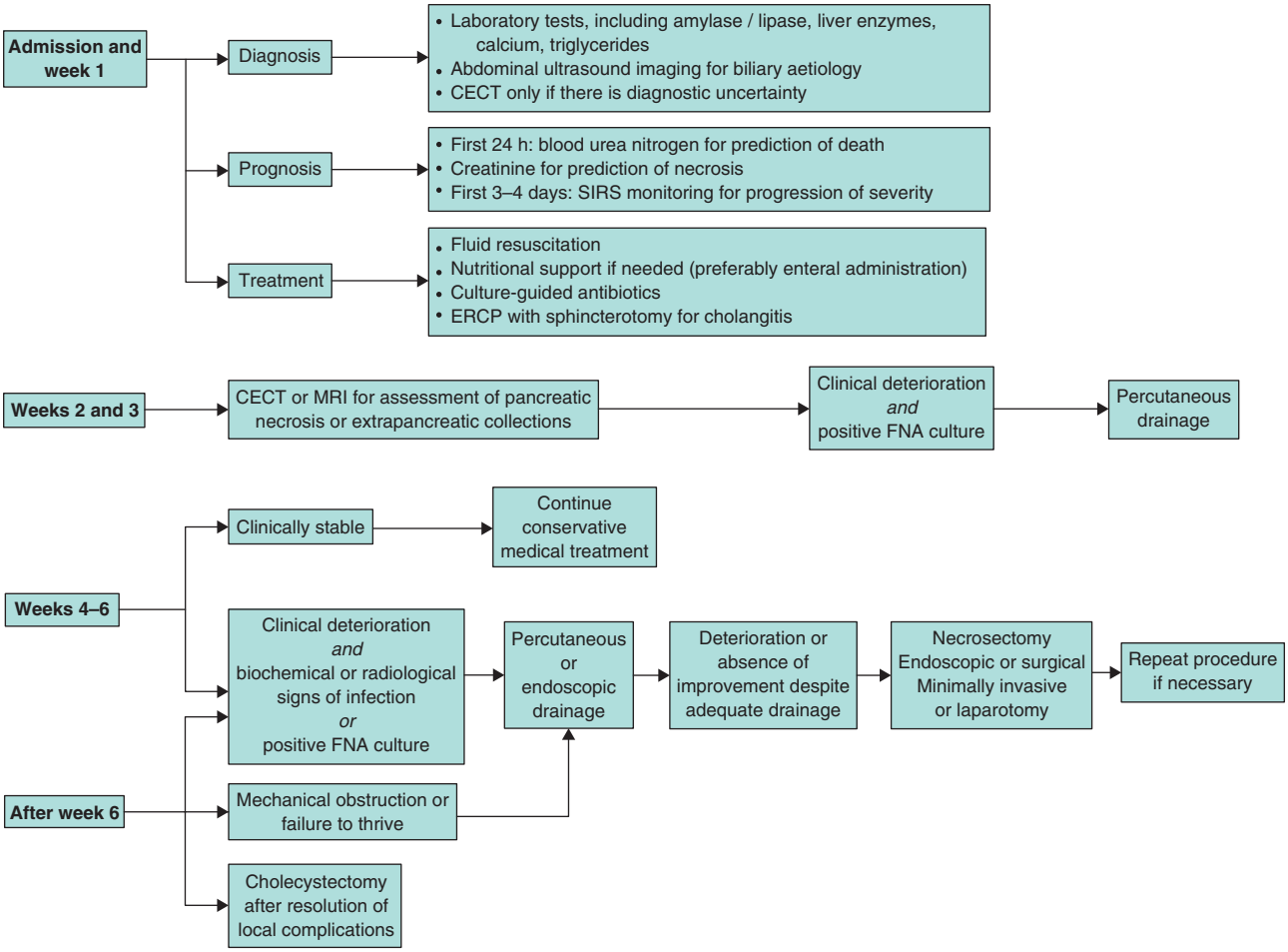


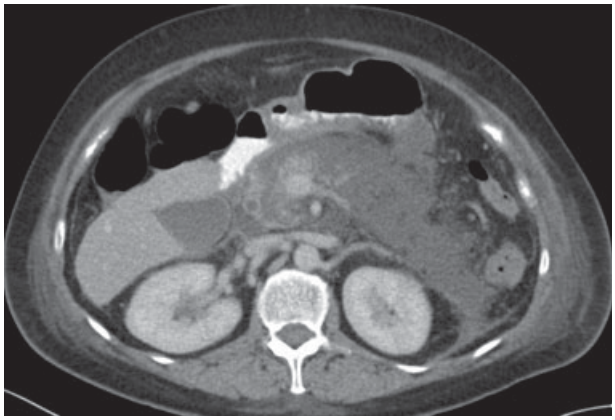
Fig. 1 Suggested treatment algorithm for necrotizing pancreatitis according to the time after onset of symptoms. CECT, contrast-enhanced computed tomography; SIRS, systemic inflammatory response syndrome; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; FNA, fine-needle aspiration

restoring the microcirculation and thereby oxygenation of the pancreas and other organ systems[56]. Adequate fluid resuscitation may prevent further local injury to the pancreas and so might inhibit the systemic inflammatory response[57–59]. Traditionally, liberal intravenous fluid infusion has been advocated. The patient's vital signs (heart rate, blood pressure, oxygen saturation) and urinary output (accepted minimum urinary output over 0·5 ml per kg bodyweight per h) are monitored, taking into account pre-existing conditions contraindicating high-volume fluid infusion[14,20,40]. Fluid resuscitation is especially important in the first 12–24 h after admission. Thereafter, the amount of fluid administered can be decreased[10]. It is unclear what type of fluid should be used. A recent systematic review[57] found no clinically significant differences between the use of isotonic crystalloid or colloid fluid.

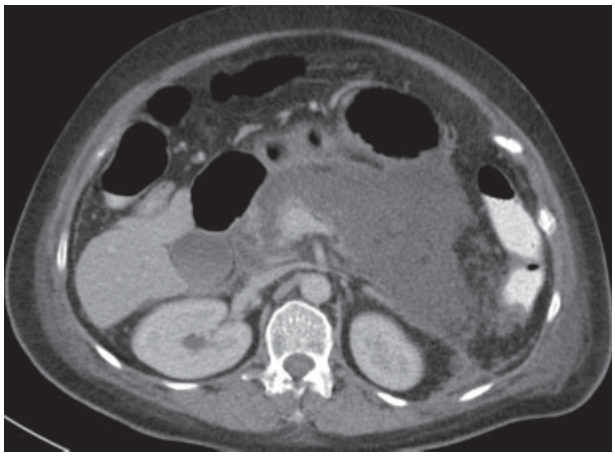
Role of endoscopic retrograde cholangiopancreatography

In gallstone pancreatitis, obstructing stones or biliary sludge usually pass through the biliary tract spontaneously[60]. Obstruction persists in some patients, increasing the risk of developing cholangitis. If progressive cholestasis and dilatation of the common bile duct is accompanied by fever, cholangitis should be suspected and urgent endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy is indicated[61,62].

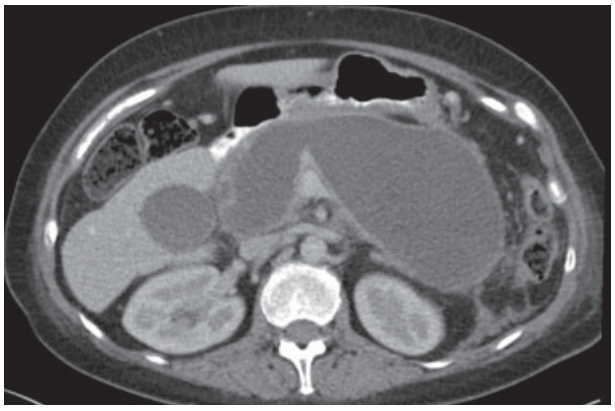
The benefit of ERCP in patients with pancreatitis without cholangitis, however, is unclear. A recent meta-analysis[63] with pooled data from seven randomized trials, including 757 patients with gallstone pancreatitis, found no significant reduction in morbidity or mortality by routine use of early ERCP (within 72 h after admission) compared



a Day 4



b Day 12



c Day 35

Fig. 2 Example of contrast-enhanced computed tomography in a patient with necrotizing pancreatitis. **a** Acute necrotic collection on day 4 after the onset of symptoms. Note the heterogeneous non-liquid pancreatic and extrapancreatic components in the retroperitoneum. **b** On day 12 after symptom onset the acute necrotic collection is not yet fully encapsulated. **c** On day 35 after symptom onset note the enhancing wall of reactive tissue or encapsulation; this is an example of walled-off necrosis

with conservative treatment. Unfortunately, the subgroup of patients with predicted severe pancreatitis was relatively small, raising the possibility of a type II error. Further research is needed in this group of patients. Recently, a new randomized multicentre trial has been started in the Netherlands investigating routine early ERCP with sphincterotomy in patients with predicted severe biliary pancreatitis (APEC trial; ISRCTN97372133).

Nutrition

In necrotizing pancreatitis, adequate nutritional intake can be obtained through an oral diet or enteral nutrition. Several meta-analyses[64–66] of randomized trials comparing enteral with parenteral nutrition showed that enteral nutrition significantly reduces organ failure, infections and mortality. Two small randomized studies[67,68], with 31 and 50 patients with severe pancreatitis, concluded that nasogastric feeding was just as well tolerated as nasojejunal feeding. No differences were found between different types of enteral nutrition formulation[69].

Enteral feeding is hypothesized to maintain the integrity of the gastrointestinal mucosal barrier, thus inhibiting bacterial translocation and reducing infectious complications[70–73]. Several non-randomized studies[74,75] concluded that very early enteral feeding (within 24–48 h after onset) reduces pancreatic infections and multiple organ failure even further. The results are awaited from a multicentre trial[76] investigating the effect of very early enteral feeding in patients with predicted severe pancreatitis. In this trial, 208 patients were assigned randomly to very early nasojejunal feeding (within 24 h after onset) or standard practice (oral nutrition on demand or, if needed, enteral feeding after 72 h).

Antibiotic prophylaxis

Secondary infection of pancreatic or extrapancreatic necrosis occurs in approximately one-third of patients with necrotizing pancreatitis[7,77,78]. Many efforts have been made to test antibiotic prophylaxis in prevention of infected pancreatic necrosis. Early small randomized trials[79,80] showed promising results, reporting lower rates of mortality and infected necrosis. More recent placebo-controlled studies[81–83], however, failed to confirm these results. In the past 5 years, ten meta-analyses[78,84–92] have been published on the subject. Eight of these did not find a reduction in infected pancreatic necrosis and none showed a reduction in mortality. These clinical studies have been critiqued for their low methodological quality[93]. So far, three double-blind and placebo-controlled studies[81–83]

have been performed, showing no positive effects of antibiotic prophylaxis.

In the first week after admission, there is no role for routine antibiotic prophylaxis in the treatment of necrotizing pancreatitis. Antibiotics should be withheld until infection is proven with positive cultures. In most patients, infection of pancreatic or extrapancreatic necrosis does not occur until week 3 or 4. Antimicrobial agents with favourable pancreatic tissue penetration, such as carbapenems, metronidazole and quinolones, are recommended[10,80,83].

Abdominal compartment syndrome

Abdominal compartment syndrome (ACS) is rare in patients with necrotizing pancreatitis and, if the suspicion arises, it occurs most often in the first week after symptom onset[94]. Aggressive fluid resuscitation, retroperitoneal fluid accumulation and ascites may contribute to raised intra-abdominal pressure (transvesical pressure measurements exceeding 12 mmHg). A prevalence of intra-abdominal hypertension of up to 61 per cent has been reported in patients with necrotizing pancreatitis[95]. Persisting intra-abdominal hypertension is believed to be a precursor of ACS. The World Society of the Abdominal Compartment Syndrome[96] defines ACS as 'persisting abdominal pressure above 20 mmHg accompanied by new onset organ failure'.

Several non-invasive strategies may aid in reducing the intra-abdominal pressure: enteral decompression through gastric or rectal tubes, recalibrating the intravenous fluid regimen for a zero-to-negative balance, and increasing abdominal wall compliance through medication. If non-invasive options are not sufficiently effective, the next step of treatment should be aimed at evacuation of excess intra-abdominal or retroperitoneal free fluids, such as ascites, by percutaneous catheter drainage (PCD).

Decompression laparotomy is sometimes applied as a 'last resort' if multiple organ failure escalates. However, currently there is no evidence that surgical decompression has a beneficial effect on outcome. If there is no infected necrosis (as in most patients during the first week after admission) the retroperitoneum should not be opened during this procedure to minimize the risk of introducing pathogens[96,97].

Although decompression laparotomy seems effective in individuals without pancreatitis[13,98], ACS in patients with pancreatitis seems associated mainly with massive fluid resuscitation[99]. In these patients, no improvement in overall morbidity and mortality has been documented. A randomized trial is currently investigating the role of percutaneous drainage as a primary means of decompression compared with surgical decompression (DECOMPRESS trial; ClinicalTrials.gov NCT00793715)[100].

Management during the second and third weeks

Infection of pancreatic necrosis

Infected pancreatic necrosis is usually diagnosed during the second or third week after onset[48,81,101]. Other possible sources of infection, such as pneumonia, must be ruled out first, as these tend to occur earlier in the course of the disease[48]. Cross-sectional imaging is indicated to assess the evolution of pancreatic necrosis and peripancreatic fluid collections. Occasionally, CT or MRI may reveal retroperitoneal gas bubbles inside pancreatic fluid collections pathognomonic for infection. These collections rarely show signs of complete encapsulation before the fourth week[102].

Fine-needle aspiration

Fine-needle aspiration (FNA) culture of pancreatic fluid collections is useful if the diagnosis is uncertain, and has the added value of optimizing antibacterial therapy. Routine FNA culture was promoted more widely in the past, but has been used more selectively in recent years. The reason for this shift is that, with the more conservative approach currently advocated, FNA results less often lead to a change in management and so aspiration is indicated less frequently. FNA carries a risk of false-negative results in up to 25 per cent depending on timing after onset and indication[103,104]. Therefore, FNA should be used to obtain information about a collection only when the result will direct the treatment plan. FNA is warranted, for instance, in patients who fail to recover from organ failure (and thus have persisting high inflammatory parameters so that infected pancreatic necrosis cannot be discriminated clinically) and without signs of infection on CECT. A positive FNA would warrant a step up in treatment of the fluid collection.

Percutaneous catheter drainage

PCD (*Fig. 3*) is an important adjunct in the care of patients with infection of acute necrotic collections or walled-off necrosis. Once infection occurs, the patient must be treated effectively in a timely manner for a good outcome. Most patients need antibiotics and drainage. The use of PCD is the first step of the step-up approach. Catheters are placed optimally by the left or right retroperitoneal route, depending on the anatomy of the collections. In the absence of solid evidence regarding the optimal timing

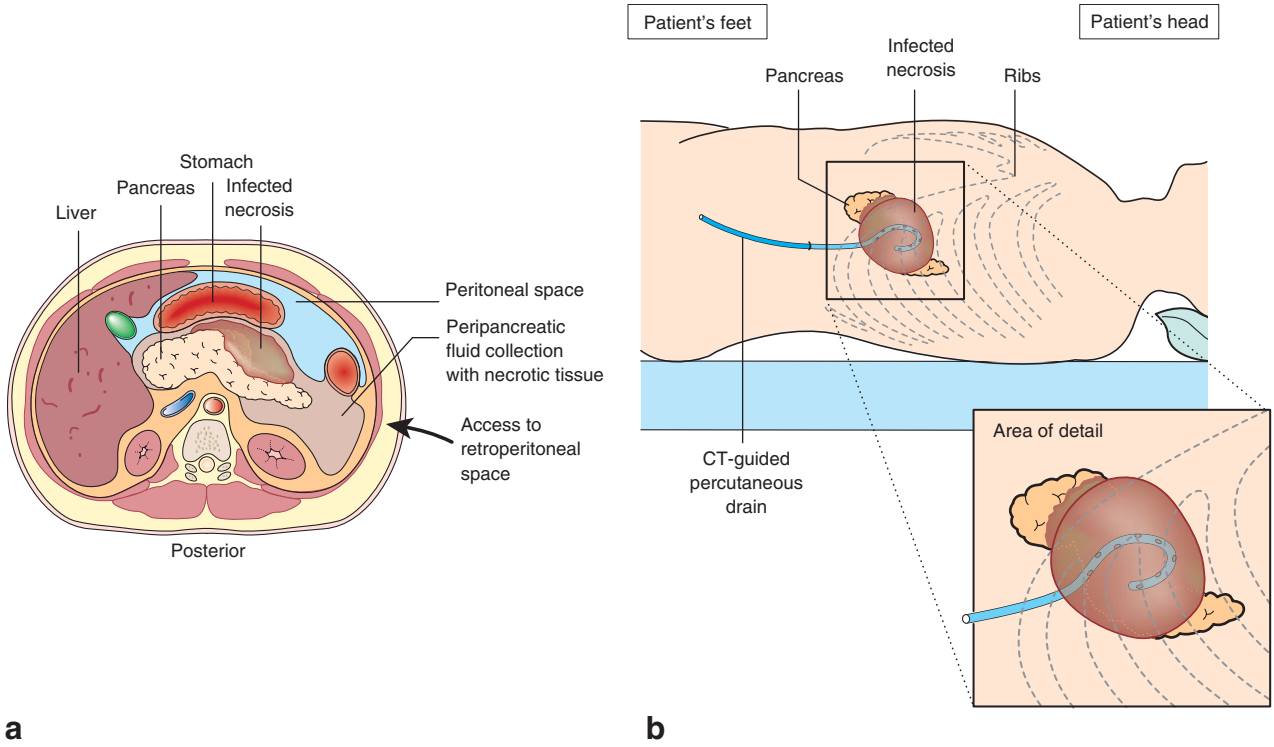


Fig. 3 Preferred route for percutaneous catheter placement for drainage of a typical infected peripancreatic collection. Via the left flank, a catheter can be manoeuvred retroperitoneally between the spleen, descending colon and kidney using computed tomography (CT) guidance

of PCD, different strategies are applied. A positive FNA culture during the second or third week leads to PCD in some institutions, whereas in others antibiotics are started first, with PCD in this disease phase only following further clinical deterioration. Early PCD may substantially improve a patient's condition but can also introduce infection in a sterile collection, thereby leading to deterioration, so it is important that infection be documented clearly first.

In the past decade, several specialized centres have reported successful treatment of infected necrotizing pancreatitis with PCD alone in 35–55 per cent of patients[105–107]. The PANTER trial compared PCD as the first step of a step-up approach with primary open necrosectomy for infected necrotizing pancreatitis. Interestingly, more than 30 per cent of those enrolled in the step-up group did not need additional surgical necrosectomy[107]. Available evidence indicates that a subgroup of patients with infected necrotizing pancreatitis can be treated successfully with PCD alone. Unfortunately, it remains unclear which patients will recover successfully after PCD alone and which will need an additional endoscopic or surgical necrosectomy. Therefore, the first step in treatment should be percutaneous or endoscopic drainage, followed by surgical or endoscopic necrosectomy only if clinically necessary.

Management during the fourth, fifth and sixth weeks

A second peak in mortality is seen in this phase of the disease, mostly associated with infection of the pancreatic or extrapancreatic necrosis[14]. In general, only patients with infected necrosis should undergo invasive interventions[14,20,108]. Interventions such as endoscopic transluminal drainage and necrosectomy, and minimally invasive or open necrosectomy should be delayed if possible to around 4 weeks after the onset of symptoms[102]. This allows the collection to become walled-off, which is believed to facilitate necrosectomy[9] (*Fig. 2*).

Minimally invasive surgical necrosectomy

Two minimally invasive surgical techniques have gained widespread acceptance: sinus tract endoscopy (also referred to as minimal access retroperitoneal pancreatic necrosectomy, MARPN)[109,110] and video-assisted retroperitoneal

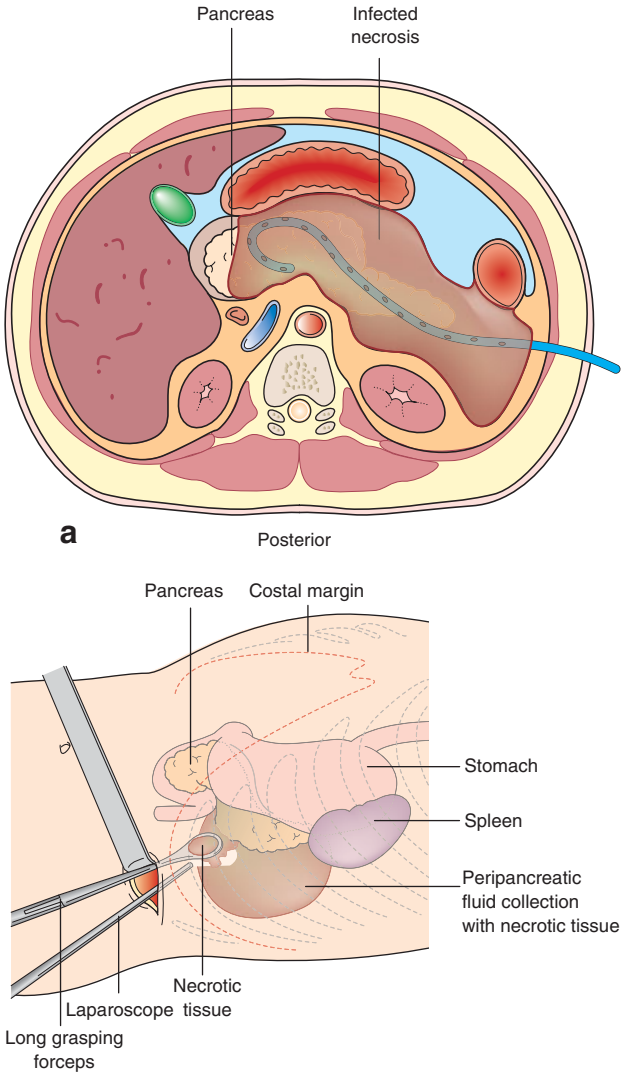


Fig. 4 Video-assisted retroperitoneal debridement. **a** Using the percutaneous catheter as retroperitoneal guide, a 5-cm subcostal incision is made. **b** The first solid debris that is encountered can be removed bluntly using a long grasping forceps. Subsequently a 0° laparoscope is introduced into the necrotic cavity and more central necrotic debris can be removed

debridement (VARD)[106] (*Fig. 4*). In both procedures, access to the necrotic pancreas is achieved by following the tract of a radiologically placed drainage catheter.

In sinus tract endoscopy, pioneered in the Glasgow Royal Infirmary, Glasgow, UK, a nephroscope is inserted into the infected collection after dilatation of the drain tract to 30 Fr under fluoroscopic guidance. Debridement is carried out using a long forceps, and the necrotic cavity is flushed using jet irrigation and suction devices. The procedure is repeated if the patient fails to recover and residual infected necrosis is suspected. A median of three to five procedures is needed for adequate necrosectomy[109,110]. A large retrospective cohort series indicated that survival rates are potentially better with MARPN compared with open necrosectomy (mortality rate: 19 per cent of 137 patients *versus* 38 per cent of 52 patients)[111]. Additionally, postoperative organ failure and complication rates may be lower in the minimally invasive group.

The VARD technique was developed in the University of Washington Medical Center, Seattle, Washington, USA. It uses a 5-cm subcostal incision in the left flank near the exit point of the percutaneous drain[112]. The drain is followed closely into the collection. After opening the collection bluntly and clearing the first liquid and solid debris encountered with suction and a long grasping forceps, a 0° camera used for laparoscopy is introduced into the necrotic cavity. The camera is placed through a laparoscopic port, which is placed directly through the incision. Carbon dioxide is infused through the percutaneous drain to inflate the cavity. After surgery continuous lavage is started using two large-diameter drains. This technique allows vigorous debridement of the necrotic cavity with a median of one procedure[106]. In the years following the introduction of VARD in Seattle, it became clear that percutaneous drainage alone could also be sufficient in some patients, instead of just serving as a bridge to necrosectomy. This finding generated the hypothesis behind the PANTER trial[113]. In this trial, 88 patients were allocated randomly to either primary necrosectomy via laparotomy or the step-up approach. A significantly lower rate of the composite endpoint of major morbidity or death was found in the step-up group (40 *versus* 69 per cent; $P = 0{\cdot}006$). New-onset multiple organ failure was also significantly less common in the step-up group (12 *versus* 40 per cent; $P = 0{\cdot}002$).

A few case series have been published on laparoscopic necrosectomy. This transperitoneal route offers access to the lesser sac and simultaneous management of intra-abdominal organs (for example concurrent cholecystectomy)[114]. However, it also has the disadvantage of introducing a continuum between the peritoneal cavity and the retroperitoneum containing infected pancreatic necrosis[112,114,115].

Endoscopic transluminal drainage or necrosectomy

Parallel to the development of minimally invasive surgical strategies, endoscopic transluminal approaches have been developed[116,117]. Under direct vision or endoscopic ultrasound guidance, the gastric or duodenal wall is punctured to reach the walled-off necrosis (*Fig. 5*). The

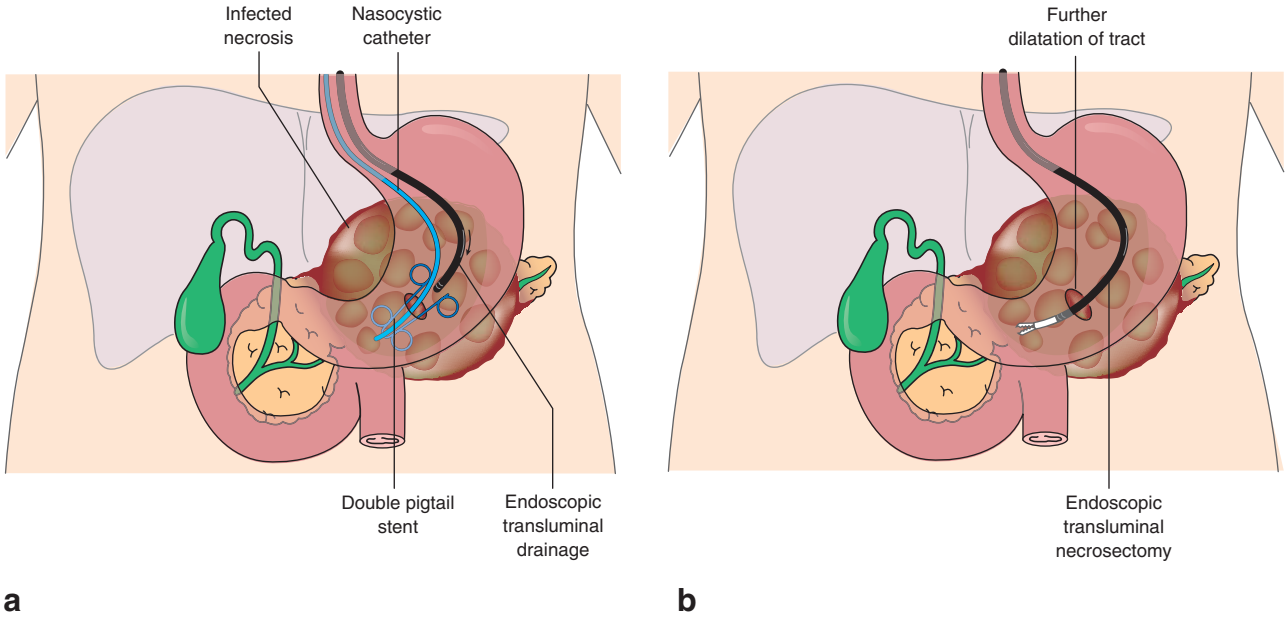


Fig. 5 Under direct vision or endosonographic guidance, the gastric or duodenal wall is punctured to evacuate the infected necrotic material. **a** After serial dilatation of this transluminal tract, two double-pigtail catheters are placed to establish a patent drain tract. **b** Should the need for endoscopic necrosectomy arise, the tract is dilated further so that various endoscopic necrosectomy instruments can be introduced

transluminal tract is dilated sequentially using a balloon. Short pigtail catheter drains or a stent can be used to prevent the access to the retroperitoneum from closing after the first procedure. A nasocystic catheter is placed in the necrotic cavity for continuous irrigation[46]. The use of multiple transluminal gateways has been suggested to improve drainage of the infected material, and successful drainage without the need for additional interventions was achieved in up to 90 per cent in a small cohort of selected patients[118]. Patients in whom endoscopic drainage proves insufficient may benefit from endoscopic necrosectomy. Like sinus tract endoscopy, the transluminal drain tract is dilated further for introduction of an endoscope. Various instruments are used for the actual necrosectomy, such as endoscopic baskets, snares, jet irrigation and forceps[117,119]. A recent systematic review[117] showed that 197 (75·8 per cent) of 260 patients were treated with endoscopic treatment alone, with only two reported deaths. Although these results seem promising, they must be interpreted with caution as they are based predominantly on non-randomized findings in selected patients from experienced institutions. The first randomized trial[52] compared endoscopic necrosectomy with surgical necrosectomy in 22 patients with infected necrotizing pancreatitis. This pilot trial showed that the inflammatory response (interleukin 6 levels) and a composite endpoint of death or major complications were significantly reduced following endoscopy compared with surgery. A large clinical trial following on from this pilot study is currently being conducted. Ninety-eight patients will be randomized to an endoscopic step-up approach or the surgical step-up equivalent (percutaneous drainage followed by VARD or, if not feasible, open necrosectomy) (TENSION trial; ISRCTN 09186711).

Open surgical necrosectomy

Primary open surgical necrosectomy has been the standard treatment of infected necrosis for decades. The classical approach is to enter the retroperitoneum through a laparotomy, after which the necrotic tissue is removed by blunt dissection[120]. Healthy pancreatic tissue is preserved as much as possible, and by doing so the risk of postoperative bleeding or pancreatic fistula is minimized. Different surgical techniques have been developed over the years, such as open packing, closed packing with planned reoperation or postoperative continuous lavage to remove any residual material[108]. Open necrosectomy remains associated with substantial morbidity[121–123]. These high morbidity rates are generally attributed to the exacerbation of stress induced by the trauma of surgery in an already critically ill patient, but are also closely associated with

the timing of intervention and the presence of persistent organ failure[107,109,124]. The minimally invasive approaches were developed specifically for this reason, although to date no randomized trial has proven the superiority of minimally invasive techniques over open necrosectomy (or laparotomy).

Management after the sixth week

Patients without proof of infection (even after negative FNA culture) who fail to recover, despite prolonged maximal supportive care, are suspected of sustaining a low-grade infection. In a recent study[104] operative cultures showed proof of infection in 42 per cent of 53 patients who had surgery because they remained persistently unwell despite negative FNA results. Patients in whom a sterile fluid collection causes clinically significant morbidity (gastric or biliary outlet obstruction, pain) should be considered for surgical or endoscopic necrosectomy. A recent randomized trial[125] comprising 40 patients compared endoscopic and open surgical cystogastrostomy. No significant differences were found with respect to recurrence of the fluid collection, reinterventions or complications. Endoscopic cystogastrostomy was associated with a significantly shorter hospital stay (median 2 days *versus* 6 days after open surgery).

Anecdotal evidence exists of spontaneous remission of necrotic collections, even when infection has been proven[116,126]. These reports suggest that in highly selected cases infected pancreatic necrosis can be managed through supportive therapy alone.

Cholecystectomy or, if not deemed feasible, ERCP with sphincterotomy should be considered to minimize the risk of recurrent biliary pancreatitis and other gallstone-related disease. It is generally recommended to postpone intervention until all radiological and biochemical signs of inflammation have subsided[127].

Finally, several other complications may occur during this phase. Vascular complications may be seen on CECT, such as splenic or portal vein thrombosis or, less commonly, splenic artery pseudoaneurysm. These must be dealt with using appropriate application of anticoagulant therapy, endovascular coiling, stenting or embolization, or sometimes even splenectomy. Pancreatic fistulas to various organs may also occur and can be treated quite successfully by endoscopic papillary stenting, thus facilitating drainage of the pancreatic secretion into the duodenum[128].

The impact of the disease and its complications on individual patients often reverberates for years. Psychological as well as physical sequelae, such as exocrine or endocrine insufficiency, may cause lifelong morbidity.

Future directions for research and improvement of outcomes

Frequent clinical evaluation of the patient's condition is of paramount importance at the earliest stages of the disease, as current predictive scoring systems have a mediocre accuracy. New biomarkers may better predict complications in the coming years. However, early adequate resuscitation in an attempt to prevent organ failure and early detection of any organ failure will remain most important. Based on current literature, liberal goal-directed fluid resuscitation and early enteral nutrition should be provided. Emergency ERCP with sphincterotomy is indicated when cholangitis is suspected, but it is unclear whether it is appropriate for patients with predicted severe biliary pancreatitis. Antibiotic therapy does not prevent infection of necrosis but is indicated if there is proven infection. ACS might occur early in the disease course, and in some critically ill patients decompression laparotomy may improve organ dysfunction temporarily if all non-surgical methods fail, although there is no solid evidence to support this.

In recent years, treatment of infected necrotizing pancreatitis has shifted from early open debridement to postponed minimally invasive step-up strategies, with initial catheter drainage only if needed followed by surgical or endoscopic necrosectomy. As PCD is a relatively simple intervention, this new strategy provides clinicians in general and district hospitals with the tools to perform the first step in treatment. Although widespread adaptation of the step-up strategy should be stimulated, it must be stressed that the presence of a multidisciplinary team of physicians is crucial in the treatment of necrotizing pancreatitis. Only a multidisciplinary team including a surgeon, gastroenterologist, radiologist and intensivist will provide adequate care during all disease phases. If such a team is not available around the clock, early transfer of the patient to an expert centre is advised. Several ongoing randomized trials will provide needed recommendations on timing of nutrition, indication for ERCP, optimal route of necrosectomy and indication for decompression in the foreseeable future.

Acknowledgements

O.J.B. is sponsored by the Netherlands Organization for Health Research and Development (ZonMw, grant number 17099.2902) and D.W.daC. by the Dutch Society for Gastroenterology (MLDS, WO 11-03) to perform clinical studies on necrotizing pancreatitis. The sponsors had no involvement in any stage of the study design, data collection, data analysis or interpretation of the study results.
Disclosure: The authors declare no conflict of interest.

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