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Necrotizing Pancreatitis

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Necrotizing pancreatitis continues to challenge clinicians, and few other medical subjects currently elicit as much debate. Parenchymal necrosis, as a complication of acute pancreatitis, occurs in 10% to 25% of patients requiring hospital admission, and continues to be associated with a mortality rate of approximately 25% [1]. Host characteristics or underlying differences in pathophysiology that lead to pancreatic necrosis remain poorly understood.

Severe pancreatitis follows a two-phase clinical course. The early first phase manifests the features of the systemic inflammatory response syndrome, and the second late phase is characterized by infectious complications. This article presents a multidisciplinary literature-based approach to the treatment of patients with necrotizing pancreatitis.

INITIAL DISEASE SEVERITY ASSESSMENT AND MANAGEMENT

The diagnosis of acute pancreatitis remains straightforward and easily confirmed, and most of these patients (approximately 80%) experience a relatively benign clinical course. The real challenge in initial management is early identification of the patient destined for systemic manifestations. The underlying cause of pancreatitis is not predictive of subsequent complications, and there is a lack of predictors of necrosis. Beginning with Ranson and Pasternack's [2] publication describing 11 objective criteria capable of predicting mortality that included five items easily measured on presentation, many authors have proposed increasingly complex risk stratification tools capable of predicting pancreatitis-related morbidity and mortality. These algorithms have not found their way into routine clinical practice, however, and most experienced clinicians continue to rely on Ranson's criteria committed to memory to guide initial clinical management.

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These key initial decision-making points include determining the level of nursing care and monitoring necessary, anticipating the required volume of resuscitative fluids, and exploring potential complications in a cost-effective manner. The authors' general practice and recommendation is to manage patients with three or more positive Ranson's criteria or an APACHE II Score greater than 7 in an ICU. Initial care of these patients is centered on adequate saline resuscitation, often guided by invasive hemodynamic monitoring and support of organ dysfunction.

MANAGEMENT OF THE PATIENT WITH SEVERE PANCREATITIS: EARLY PHASE INTERVENTIONS

Diagnosis of Pancreatic Necrosis: Role of Imaging

Pancreatic necrosis has been defined by the International Symposium on Acute Pancreatitis in 1992 as the presence of one or more diffuse or focal areas of nonviable pancreatic parenchyma. Pancreatic glandular necrosis is always associated with inflammation and often necrosis of peripancreatic fat in the mesentery and retroperitoneum (Fig. 1).

Although pancreatic necrosis may be identified at surgery or autopsy, cross-sectional imaging, especially CT, allows confident noninvasive assessment. The hallmark of pancreatic necrosis is lack of pancreatic parenchymal enhancement in a bolus contrast-enhanced CT scan. Contrast-enhanced CT is considered the reference standard for the noninvasive diagnosis of necrosis, with an accuracy of greater than 90%. Magnetic resonance imaging can assess necrosis if intravenous contrast is contraindicated [3]. CT allows assessment of the extent of glandular necrosis and the presence and extent of peripancreatic fluid collections. Multisystem impairment may be suggested by CT evidence of pulmonary edema, pleural effusions, anasarca, and diminished renal enhancement. Infected pancreatic necrosis is indicated by the presence of multiloculated gas within the gland and surrounding tissues (Fig. 2A–C). All of these CT criteria have been incorporated into various CT staging schemes, such as those presented by Balthazar and colleagues [4], and these have strong predictive value in correlating with patient morbidity and mortality. In practice, the authors may not commit the Balthazar or Ranson criteria to memory or assign a "score," but they do incorporate these objective criteria into their assessment of the patient with acute severe pancreatitis.

Although parenchymal nonenhancement accompanied by multilocular gas is essentially diagnostic of infected pancreatic necrosis, absence of gas does not exclude infection. When clinical signs and symptoms suggest pancreatic infection or necrosis, repeat CT evaluation is warranted. CT- (or ultrasound) guided fine-needle aspiration of the pancreatic bed is often required for early confirmation of infected necrosis (see Fig. 1D).

Image-guided placement of drainage catheters may help to decompress infected pancreatic fluid collections, but surgical debridement is usually required to remove the semi-solid necrotic debris (Fig. 2D, E). On occasion, the authors have used a percutaneously placed catheter as a guide to follow into the pancreatic bed when surgery is subsequently performed.

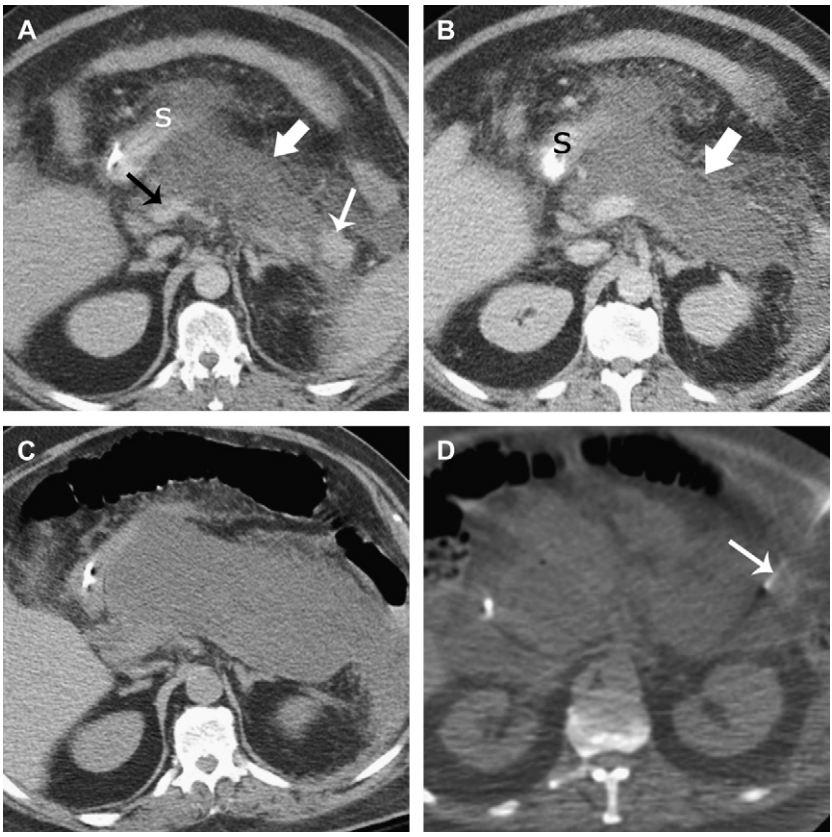
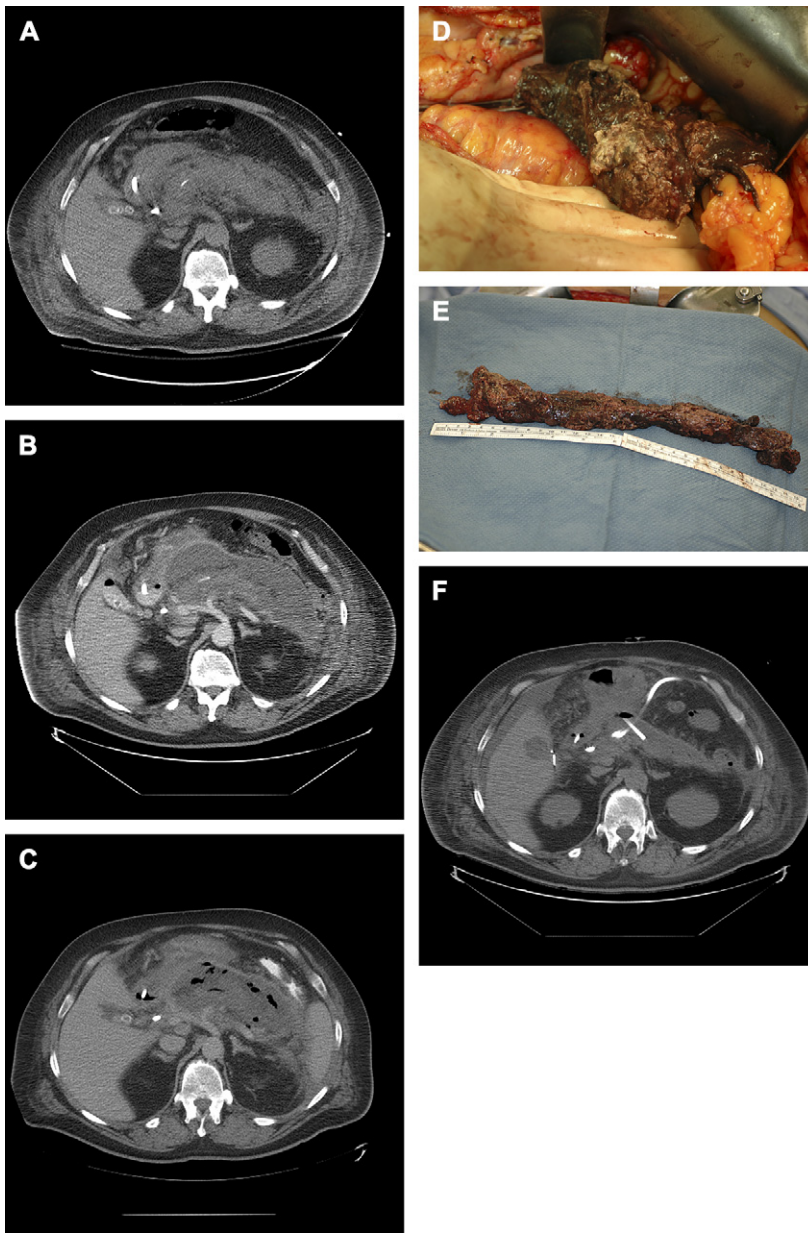


Fig. 1. A 67-year-old man with gallstone-induced pancreatitis. (*A*) Contrast-enhanced CT section on the day of admission (December 2nd) shows lack of enhancement of the pancreatic parenchyma (*thick white arrow*). A small ''island'' of normally enhancing pancreas is present in the tail segment (*thin white arrow*). Black arrow, splenic-portal confluence; S, stomach. (*B*) Repeat contrast-enhanced CT scan 7 days later (December 9th) shows extension of the inflammation and necrosis into the mesentery and retroperitoneal fat planes. The entire gland (*arrow*) is now necrotic. S, stomach. (*C*) Repeat nonenhanced CT scan 18 days after admission (December 20th) shows a more homogeneous collection of fluid and debris within the pancreatic bed. (*D*) A thin needle (*arrow*) was placed under CT guidance for aspiration of a sample of fluid from the pancreas on December 22nd. The fluid was culture-positive for bacteria.

The use of Prophylactic Antibiotics

Infection occurs in 20% to 40% of patients with necrotizing pancreatitis [5,6], and a number of small randomized prospective studies have suggested possible benefit to prophylactic antibiotic administration in patients with evidence of pancreatic necrosis. The extent of necrosis is predictive of the risk of subsequent infection (Table 1) [7]. Imipenem-cilastin was the first antibiotic agent shown to be effective in reducing infectious complications in this patient

population [8]. More recent data have shown that imipenem-cilastin is superior to perfloxacin [9], and that the alternative regimen of a fluoroquinolone combined with metronidazole often used in patients with a penicillin allergy is inadequate [6]. In the authors' institution a 2-week course of imipenem-cilastin



is recommended for patients with necrotizing pancreatitis. Recent data suggest there may be benefit to the initiation of therapy on admission, rather than after necrosis as a complication has been identified [10].

Candida infection complicates severe pancreatitis in 8% to 15% of patients [1], and concern has been raised that the use of prophylactic antibiotics predisposes patients to fungal infections, yet this fear has not been substantiated by clinical investigation [11]. As such, the coadministration of antifungal preparations is controversial.

Nutrition

Recently, there has been great clinical interest in the aggressive use of enteral nutrition delivered distal to the ligament of Treitz in patients with severe pancreatitis. This topic is addressed in detail elsewhere in this issue. Briefly, the value of enteral nutrition to gut-barrier function is well established, and most infectious complications encountered in patients with severe pancreatitis are caused by enteric organisms. It is not surprising that recent reports suggest that enteral nutrition for patients with severe pancreatitis is safe and associated with reduced rates of infectious complications [12]. Mortality rates, however, have not yet been shown to decrease [12]. Presently and in contrast to past opinion, most experts believe total parenteral nutrition should be avoided in lieu of postpyloric enteral nutrition with an elemental formula. Although additional investigation is warranted, it is also important to note that this

Fig. 2. A 62-year-old man with gallstone-induced pancreatitis. (*A*) The patient developed acute respiratory and renal insufficiency, and was maintained on enteral nutrition and intravenous imipenem and fluconazole. This CT scan performed 10 days after onset of symptoms (December 24th) and without intravenous contrast because of his renal failure shows generalized edema of the peripancreatic fat planes in a pattern essentially diagnostic of acute pancreatitis. The absence of intravenous contrast material precludes evaluation for pancreatic necrosis. The pancreas seems to be fairly homogeneous, however, and no large pancreatic or peripancreatic fluid collections or foci of extra luminal gas are identified. (*B*) On a follow-up contrast-enhanced CT obtained on January 4th after resolution of the patient's acute renal failure, minimal enhancing pancreatic parenchyma can be identified. An evolving lesser sac inflammatory process is evident. (*C*) The patient recovered from multiorgan system dysfunction and was discharged home 27 days after onset of symptoms. At home he was maintained on clear liquids supplemented by nasojejunal feedings. He returned 23 days later (50 days after onset of his symptoms) with complaints of intermittent fevers. His white blood count was normal but his CT scan shows a large collection replacing most the pancreatic body tail and head. Although not significantly changed in size or extent it now contains numerous internal gas bubbles throughout all portions, signifying infection of this area. (*D*) Exploration of the lesser sac revealed a small amount of fluid and extensive necrotic tissue. The necrotic tissue was well demarcated from surrounding viable tissues, and could be easily separated from these viable tissues using gentle blunt dissection. The necrotic tissue was delivered upward from the lesser sac, beginning with the left-sided tissues. (*E*) With gentle manipulation, the necrotic tissue could be delivered out as a single intact specimen comprising virtually the entire pancreas tissue. (*F*) A follow-up CT scan obtained 9 days after the pancreatic debridement procedure shows virtually complete removal of the necrotic tissues. Two drains can be seen lying in the lesser sac.

Table 1
Relationship of extent of necrosis to risk of infection

% Extent of Necrosis	% Sterile	% Infection	*P* Value
<30 of the pancreas	56	10	<.00001
30–50 of the pancreas	28	10	NS
>50 of the pancreas	16	80	<.00001

Adapted from Buchler MW, Gloor B, Muller CA, et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg 2000;232:623; with permission.

observation has led some to question the value of prophylactic antibiotics in patients who are successfully nourished by enteral means.

Adrenal Insufficiency and other Medical Management Considerations

A new development in the care of critically ill patients is an appreciation of the frequency with which relative adrenal insufficiency affects these patients. Muller and colleagues recently reported that in patients with severe pancreatitis, cortisol levels decrease during the development of necrosis [13,14]. This, along with observed decreases in corticosteroid-binding globulin levels, suggests that relative adrenal insufficiency is present in patients with severe pancreatitis. Given that adrenal insufficiency is known to promote acinar cell apoptosis, the authors have further hypothesized that deficient cortisol levels may contribute to the pathophysiology of pancreatic necrosis. Presently, adrenal support in patients with severe acute pancreatitis by administration of exogenous corticoids seems reasonable, but additional investigation is necessary to determine if this intervention lowers morbidity or mortality.

A number of other interventions aimed at damping the systemic inflammatory response that characterizes the early phase of severe pancreatitis or interventions aimed at inhibiting pancreatic secretion have been clinically assessed. To date, randomized placebo-controlled studies of gabexate (Xigris), aprotinin, lexipafant, and octreotide have failed to prove medical benefit [12].

Indications for Early Operative Intervention

Early endoscopic retrograde cholangiography improves outcome in the subset of patients with biliary pancreatitis and a persistently impacted common bile duct stone [15,16]. Most current guidelines recommend endoscopic sphincterotomy when biliary obstruction or cholangitis are present. In these patients, the severity of illness results not only from the systemic inflammatory response elicited by the acute pancreatitis, but also from the concomitant cholangitis.

Perhaps the most exciting advance in the care of the early phase of severe pancreatitis comes from the recent elucidation of the systemic effects of abdominal hypertension leading to an abdominal compartment syndrome ([ACS] defined by intra-abdominal pressure >25 mm Hg). ACS results in reduced venous return and diaphragmatic excursion and leads to hemodynamic compromise, acute renal failure, and increased ventilator requirements. It has been recently reported that the in-hospital mortality rate for patients with

severe pancreatitis and ACS is 50% compared with 15% in patients without ACS [17]. Although the prevalence of ACS in severe acute pancreatitis remains unknown, it has been estimated to be present in about 40% of patients and to meet criteria for surgical decompression in up to 10% [18].

ACS is treated by decompressive laparotomy and often results in a rapid, remarkable improvement in the patient's hemodynamic status and respiratory and renal functions. Given the limited nature of the procedure and the challenges and risks encountered in attempting to transfer these critically ill patients to the operating suite, the authors have often elected to perform the laparotomy in the ICU setting. They have not encountered a need for significant support from operating room–based personnel because they typically do not explore the lesser space in this situation. A number of options are subsequently available for managing the open abdomen; the authors' group favors the use of a vacuum-assisted closing dressing.

The concept of ACS contributing to the systemic effects of severe pancreatitis segues into the controversial subject of timing of operative debridement. Is the often-observed improvement in a patient's condition after early debridement actually related to decompression of an ACS? Early debridement has been practiced at a number of high-volume tertiary medical centers, but this practice is falling out of vogue as evidence mounts that delayed surgical intervention is associated with better outcomes [19,20]. The impact of early decompressive laparotomy for ACS without concurrent pancreatic debridement on the morbidity and mortality of severe acute pancreatitis has yet to be evaluated.

MANAGEMENT OF THE PATIENT WITH SEVERE PANCREATITIS: LATE-PHASE INTERVENTIONS

The late phase of severe pancreatitis is encountered approximately 3 weeks following initial presentation but in essence occurs over a broad time frame and is characterized by infectious or hemorrhagic complications. Without surgical management the mortality in the setting of infection approaches 100%, whereas with surgical management the mortality is approximately 25%. Infected pancreatic necrosis remains a clear indication for surgical intervention. Other indications include the drainage-debridement of persistent symptomatic fluid collections, and prolonged failure-to-progress with ongoing organ dysfunction in the absence of documented infection.

Intraluminal and intra-abdominal hemorrhage are rare complications of severe pancreatitis, but remain independent predictors of mortality [21]. Operative approaches to these complications can easily result in failure caused by ongoing inflammation in the retroperitoneum impacting the dissection, and by decreased integrity of tissues resulting in their failure to hold sutures. Most high-volume centers initially manage bleeding complications angiographically. Angiography is 96% sensitive in identifying the source of hemorrhage, and embolization is feasible and successfully controls hemorrhage in approximately 60% of patients [22]. Surgical exploration for management of hemorrhage is reserved for angiographic failure.

Surgical Approaches, Timing, and Complications

The standard of care for operative management is not well established, and a number of differing approaches continue to be used. Delayed intervention (2 weeks) is associated with reduced morbidity [20]. One possible reason for this observation is that the liquefaction and demarcation of necrotic tissues facilitates a single exploration, debridement, and external drainage. Occasionally, the local inflammatory process is adequately mature to allow debridement and creation of a communication to the gastrointestinal tract in a manner similar to creation of a pancreatic cystogastrostomy. This approach allows for any residual necrotic debris to drain internally once it has become liquefied and avoids the need for external drainage that may result in a persistent pancreaticocutaneous fistula. Although this technique is most often applicable in the setting of a late infection (usually >6 weeks after initial presentation), in the setting of proved infection leading to even mild sepsis surgical intervention should not be delayed to attempt this mode of treatment.

With later surgical intervention leading to better demarcation of the extent of necrosis and maturation of the local inflammatory response, serial exploratory laparotomy with open packing has been supplanted when possible by a single exploration using smaller incisions with primary closure of the abdomen. A recent CT scan can be invaluable in guiding safe dissection and localizing small loculated pockets of fluid away from the immediate peripancreatic region. All necrotic material is debrided (Fig. 2D). Drains are left in the pancreatic bed to manage leakage of pancreatic juice, and many advocate continuous irrigation of these drains to reduce the risk of clogging and to facilitate removal of residual debris. The authors' group is divided on the use of combination sump drains. These large drains clearly are more effective in the drainage of viscous particulate effluent, but may increase the risk of erosion into surrounding structures leading to fistula formation or hemorrhage. They routinely place a combination decompressive gastrostomy–feeding jejunostomy Silastic catheter.

Early and late morbidity (Table 2) caused by wound complications and enteric fistula from exposed loops of bowel have plagued pancreatic surgeons [21,22], and fostered enthusiasm for minimally invasive approaches to infected necrotizing pancreatitis. Reported series of laparoscopic-assisted necrosectomy have shown the technique to be feasible in most patients, and associated with low morbidity and mortality [23]. Comparison with more traditional open procedures, however, has not been made.

Finally, Papachristou and colleagues have recently reported their series of patients with walled-off pancreatic necrosis treated by per oral endoscopic drainage-debridement [24]. They have reported successful treatment with this natural-orifice technique in 43 of 53 patients attempted. Adjuvant percutaneous drainage was required in 40% of the patients, and operative intervention was necessary in 20% of the patients. Morbidity was otherwise acceptable. The surgical management of infected pancreatic necrosis is currently in evolution. Active investigation should be able to determine the impact of these minimally invasive approaches on mortality, morbidity, ICU and hospital stay, and costs related to pancreatic necrosis.

Table 2
Early and late complications of surgical management of pancreatic necrosis

	Number (%)	Mortality (N)	Univariate significance (*P* Value)
Early complications			
One or more complication	82 (92)	25 (28)	NA
Organ failure	44 (50)	19	.004
Vein thrombosis	11 (13)	0	NA
Cardiovascular	14 (16)	5	NS
Pneumonia	4 (5)	2	NS
Colonic necrosis	2 (2)	2	.08
Fistulae	4 (5)	1	NS
Hemorrhage	10 (11)	7	<.01
Fungal infection	28 (32)	13	<.01
Late complications			
One or more complication	39 (62)	—	
Biliary stricture	4 (6)	—	
Pseudocyst	5 (8)	—	
Pancreatic fistula	8 (13)	—	
Gastrointestinal fistula	1 (2)	—	
Delayed fluid collection	3 (5)	—	
Incisional hernia	1 (2)	—	
Exocrine insufficiency	16 (25)	—	
Diabetes mellitus	19 (33)	—	

Adapted from Connor S, Alexakis N, Raraty MG, et al. Early and late complications after pancreatic necrosectomy. Surgery 2005;137:502, 503.

SUMMARY

Severe acute pancreatitis is a diverse disease process, and there is a relative lack of prospective randomized data to guide management. The clinical course of these patients can be demarcated into two phases: an early, aseptic inflammatory phase characterized by capillary leak and organ dysfunction, and a late phase where local or disseminated infectious complications ensue. Current best practice suggests that the early phase be managed nonoperatively, with the exception of surgical release of ACS; early necrosectomy in the absence of infection is not warranted. The use of prophylactic antibiotics is supported by current data, and this clinical practice has not been proved to result in an increased prevalence of fungal infections. The use of enteral rather than parenteral nutrition may reduce the risk of developing infected pancreatic necrosis and thereby render obsolete the current practice of administering prophylactic antibiotics. CT and fine-needle aspiration are sensitive methods to identify infection as a complication of necrosis, and this remains a definitive indication for necrosectomy. Comparisons of open repeated debridement and packing with minimally invasive or single surgical procedures with lavage favor the latter. Late complications of surgical intervention are common, however, and despite this management strategy, the mortality associated with severe acute pancreatitis remains approximately 25%.

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