Surgical Step-Up Approach in Management of Necrotizing Pancreatitis

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KEYWORDS

• Debridement • VARD • Transgastric • Necrotizing pancreatitis • Step-up

KEY POINTS

- Understanding the biology and natural history of AP is crucial to inform decision making in this complex disease process.
- Intervention in necrotizing pancreatitis is best determined by multidisciplinary evaluation; communication is paramount.
- Several approaches to intervention are effective (no "one-size-fits-all"); the key to optimal patient outcomes lies in pairing the proper approach with the appropriate patient and clinical situation.

INTRODUCTION

Necrotizing pancreatitis (NP) affects 10% to 15% of all patients suffering from acute pancreatitis. Despite improved understanding of the disease process and advances in therapeutic strategy, this complex disease is still attended by up to 15% mortality in contemporary times. Necrotizing pancreatitis provides the clinical challenges of working in a multi-disciplinary group, determining proper timing for intervention, and identifying appropriate intervention approaches based on individual patient anatomy, physiology, and local expertise. The modern treatment paradigm consists of supportive care, "stepping up" to a variety of mechanical necrosis interventions ranging from percutaneous, endoscopic, and surgical. However, a "one-size-fits-all" approach does not apply to all patients with necrotizing pancreatitis and treatment must be tailored to the individual patient. This review discusses the approach to surgical necrosis debridement in necrotizing pancreatitis.

INCIDENCE AND ETIOLOGY

Worldwide, the prevalence of acute pancreatitis has doubled over the last 3 decades and is estimated to be over 6 million cases annually.[1] Necrotizing pancreatitis

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develops in 10% to 15% of all acute pancreatitis cases and in the United States accounts for 30,000 to 60,000 cases per year.[2–5] The contemporary mortality rate in necrotizing pancreatitis ranges from 10% to 15%, despite an improved understand of the disease process and advances in therapeutic strategy.[6–9] The etiology of necrotizing pancreatitis mirrors that of acute pancreatitis, with the most common causes being biliary (20%–50% of cases) and alcohol (20%–40% of cases).[6,10,11] Additional frequently seen causes, albeit relatively less common, include hypertriglyceridemia, genetic mutations, medications, autoimmune, iatrogenic (ie, postendoscopic retrograde cholangiopancreatography), hypercalcemia, and trauma.

PATHOPHYSIOLOGY AND TREATMENT CONSIDERATIONS

The progression from acute pancreatitis to severe acute pancreatitis is attributed to the systemic inflammatory response and activation of the coagulation cascade.[12,13] Why some patients progress to necrotizing pancreatitis, but the majority develop mild acute pancreatitis is less clear, nonetheless likely stems from superfluous activation of the systemic inflammatory response and/or coagulation cascade. The human immune system and its response to antigens require a balance of proinflammatory and anti-inflammatory mediators working in concert. A summary of the key proinflammatory and anti-inflammatory mediators involved in acute pancreatitis is shown in Fig. 1. A self-limited and balanced inflammatory and anti-inflammatory response is seen in mild acute pancreatitis. In stark contrast, severe acute pancreatitis develops when an imbalance in the inflammatory response develops and proinflammatory mediators are allowed to propagate unimpeded.[12,14–17]

In necrotizing pancreatitis, enzymatic autodigestion of the pancreatic parenchyma, vascular endothelium, and surrounding tissue results in focal or diffuse nonviable pancreatic and/or peripancreatic tissue.[2] As the systemic inflammatory response is intimately associated with the coagulation cascade, the associated compromise of the pancreatic microcirculation, including arterioles, capillaries, and venules, results in ischemic changes and necrosis of the pancreas.[18–20] Pancreatic and peripancreatic necrosis further stimulates the systemic inflammatory response, amplifying the severity of the disease.[12–17] Thus, necrotizing pancreatitis is characterized by a profound systemic inflammatory response and organ failure is common, often with associated local (peri-) pancreatic complications. The morphology/distribution of necrosis is a key component in individualizing intervention to any necrotizing pancreatitis

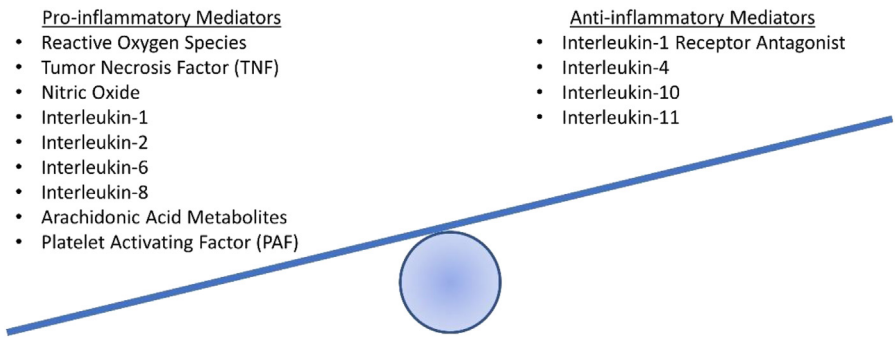

Fig. 1. Summary of the key inflammatory mediators in acute pancreatitis. An imbalance in the inflammatory response favoring proinflammatory mediators contributes to the progression of mild acute pancreatitis to severe acute pancreatitis.

patient. Beyond this, the etiology of pancreatitis and the local (peri-) pancreatic complications beyond necrosis must be considered to help guide individualized patient care. The more common local complications include mesenteric vein thrombosis, disconnected pancreatic duct syndrome (DPDS), biliary stricture, colonic complications (ischemia, perforation, fistula, stricture), duodenal complications (fistula, stricture), and visceral artery pseudoaneurysm. Finally, the overall clinical picture at the time of necrosis intervention must consider the presence of organ failure, nutritional status, and physical performance status to determine the patient's ability to tolerate certain interventions.

DEFINITIONS

An expert international consensus survey in 2012 led to the publication of the revised Atlanta classification providing distinct definitions of acute pancreatitis and its associated complications, including necrotizing pancreatitis. Organ failure in necrotizing pancreatitis is defined according to the modified Marshall scoring system for organ dysfunction, with organ failure equating to a score of 2 or greater (**Table 1**).[2,21] Necrotizing pancreatitis is diagnosed on contrast-enhanced cross-sectional imaging as the absence of pancreatic or peripancreatic enhancement.[2] In contrast, normal pancreatic parenchyma demonstrates homogenous enhancement with contrast administration (**Fig. 2**).

Disease onset is defined by the timing of symptom onset and not by the presentation to the hospital or the diagnosis of necrotizing pancreatitis.[2] This distinction is critical, as the onset of necrotizing pancreatitis is a reference point for the disease course, the development of acute/subacute complications, the timing of intervention, and the development of complications after disease resolution. It is essential to realize that the degree of pancreatic necrosis will not be appreciated on imaging the first few days after the onset of symptoms; instead, parenchymal and peripancreatic necrosis begins to become apparent after 1 week.[22,23] Patterns of necrosis in necrotizing pancreatitis may involve a combination of pancreatic and peripancreatic parenchyma, isolated peripancreatic necrosis, or, less commonly, isolated pancreatic necrosis.[24–27]

Local complications in necrotizing pancreatitis include acute necrotic collections (ANCs) and walled off necrosis (WON). An ANC is a pancreatic or peripancreatic collection with liquid and/or solid necrosis within the first 4 weeks from symptom onset

Table 1
Modified Marshall scoring system for organ dysfunction in acute pancreatitis

	Score				
Organ System	**0**	**1**	**2**	**3**	**4**
Respiratory (Pao_2/Fio_2)	>400	301–400	201–300	101–200	≤100
Renal[a] (Creatinine)	<1.4 mg/dL	1.4–1.8 mg/dL	1.9–3.6 mg/dL	3.6–4.9 mg/dL	>4.9 mg/dL
Cardiovascular[b] (systolic blood pressure)	>90 mm Hg	<90 mm/Hg, fluid responsive	<90 mm Hg, not fluid responsive	<90 mm Hg, pH<7.3	<90 mm Hg, pH<7.2

Organ failure is defined as a score of 2 or greater.

Abbreviations: dL, deciliter; Fio2, fraction of inspired oxygen; mg, milligram; mm Hg, millimeters of mercury; Pao2, partial pressure of arterial oxygen.

[a] No formal correction exists for a baseline serum creatinine greater than or equal to1.4 mg/dL.

[b] Off inotropes.

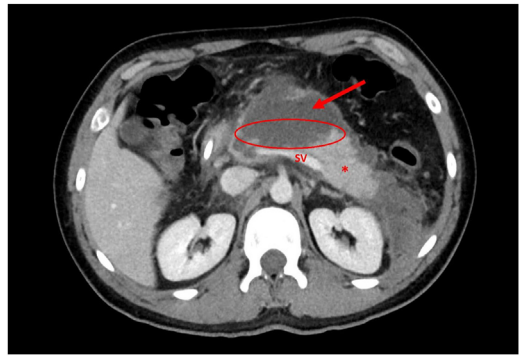

Fig. 2. Contrast-enhanced computed tomography 2 weeks after symptom onset demonstrating pancreatic parenchymal necrosis of the neck and body of the gland (*oval*) compared with normal enhancement of the tail of the pancreas (*asterisk*). Note the development of peripancreatic necrosis anterior to the gland and the development of an ANC (*arrow*).

(Fig. 3A).[2] After 4 weeks, the pancreatic and peripancreatic necrosis matures to WON, after a well-defined wall of inflammatory reactive tissue has developed (Fig. 3B).[2] In interstitial edematous pancreatitis (non-necrotizing pancreatitis), these terms must be differentiated from acute peripancreatic fluid collection (<4 weeks) and pancreatic pseudocyst (>4 weeks), respectively. It is of the utmost importance to understand the maturation phase of the pancreatic and peripancreatic necrosis, as well as the volume of solid necrosis relative to liquid necrosis. The degree of solid necrosis is difficult to determine reliably on CT scan and can be better assessed with MRI; however, the percent of solid necrosis is best estimated with endoscopic or intraoperative ultrasound.[28] Synonymous to the clinical picture of necrotizing pancreatitis, fluid collections in this disease are heterogeneous and dynamic. ANCs and WON generally liquefy over time.[28,29] Therefore, intervention later in the disease process is warranted.

Infected necrosis can be presumed in the setting of extraluminal gas in the pancreatic and/or peripancreatic necrosis on cross-sectional imaging (Fig. 4).[2] The diagnosis of infected necrosis is confirmed with positive bacteria and/or fungi on Gram stain and culture of aseptically obtained pancreatic necrosis specimens.[2] Routine percutaneous

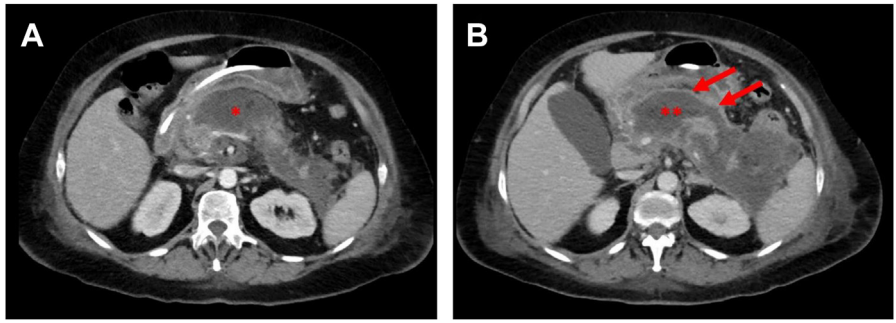

Fig. 3. Contrast-enhanced computed tomography at 2 weeks (*A*) and 2 months (*B*) in a patient with necrotizing pancreatitis. Note the transition from an ANC (*asterisk*) to walled-off necrosis (*double asterisk*) characterized by the development of a well-defined inflammatory wall of reactive tissue (*arrows*).

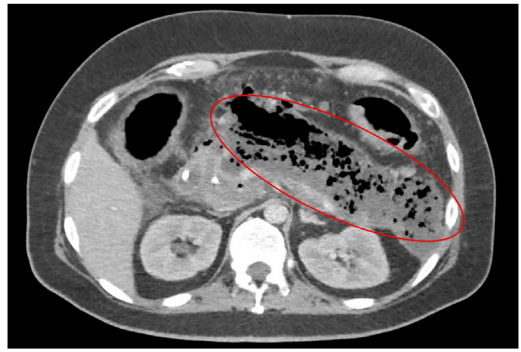

Fig. 4. Contrast-enhanced computed tomography demonstrating an infected pancreatic necrosis with diffuse gas bubbles throughout the ANC (*oval*).

fine needle aspiration (FNA) of pancreatic or peripancreatic fluid collections is only occasionally used in the current practice.[30,31] The false negative rate of FNA ranges from 12% to 25% and percutaneous aspiration has the small, but real potential to introduce bacteria/fungus to an otherwise sterile ANC/WON.[32,33]

An increasingly recognized complication of necrotizing pancreatitis is disconnected pancreatic duct (DPD) and the associated constellation of symptoms including pancreatic fistula, recurrent left-sided pancreatitis, and or recurrent pseudocyst collectively termed as DPDS.[34–36] In DPDS, pancreatic parenchyma necrosis results in viable, upstream (left-sided) pancreatic tissue whose secretions are disconnected from the normal physiologic pancreatic duct drainage. This problem is diagnosed on endoscopic or magnetic resonance pancreatography as extravasation of contrast or total cutoff of the main pancreatic duct (**Fig. 5**).[34,37,38]

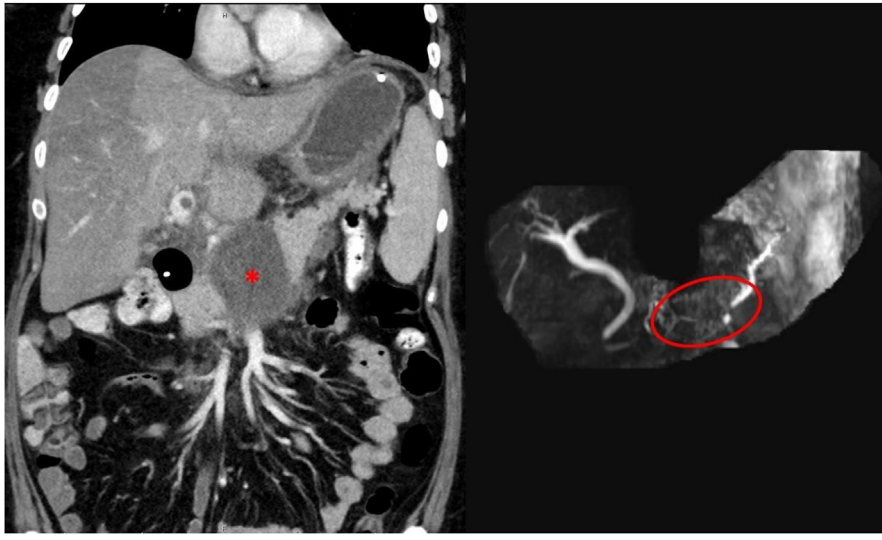

Fig. 5. Contrast-enhanced computed tomography demonstrating necrosis involving the neck of the pancreas (*left, asterisk*) resulting in cutoff of the main pancreatic duct on magnetic resonance pancreatography (*right, oval*).

CLINICAL COURSE

Two overlapping phases are often described in acute and necrotizing pancreatitis: the early phase and the late phase. These phases are associated with the 2 peaks in mortality seen during the necrotizing pancreatitis clinical course.

Early Phase

The early phase of necrotizing pancreatitis occurs during the first 1 to 2 weeks after disease onset and is associated with a profound activation of the systemic inflammatory response.[2] The initial symptomatology associated with necrotizing pancreatitis is that typical of acute pancreatitis; however, the development of pancreatic and/or peripancreatic necrosis is often associated with clinical deterioration. A variety of clinical factors (C-reactive protein, procalcitonin, computed tomography severity index) and severity scores (Ranson's criteria, Acute Physiology and Chronic Health Evaluation II Score, Bedside Index of Severity in Acute Pancreatitis, Japanese Severity Score) have been shown to predict the severity of pancreatitis[5,39–43]; regardless, treatment during the early phase is strictly supportive.

Patients with necrotizing pancreatitis typically require aggressive fluid resuscitation due to substantial third-space loss and intravascular volume depletion. Goal-directed resuscitation with Lactated Ringer's solution is standard therapy with the resuscitative phase tailored to the individual patient.[31] Supportive care in the intensive care unit is often warranted. Early organ failure (respiratory, renal, and or cardiovascular) is present in up to 25% to 35% of patients.[7,44] Early enteral nutrition is advocated in all pancreatitis patients, but clinicians must consider the discrete clinical scenario, as enteral nutrition may be poorly tolerated in necrotizing pancreatitis secondary to reactive ileus.[30,31,45] Patients not tolerating enteral nutrition warrant total parenteral nutrition as the catabolic state of necrotizing pancreatitis can rapidly produce malnutrition.[30,31] Many patients may tolerate partial enteral nutrition in the early course and the remainder of their calories may be supplemented parenterally. Gastric ileus is common with inflammation in the lesser sac, and duodenal narrowing from extrinsic pressure develops in a small subset of necrotizing pancreatitis patients.[46] Gastrojejunostomy feeding tubes are effective, permitting "venting" of the stomach and downstream enteral feeding, but may be associated with more severe complications when compared with nasojejunal feeding tubes, thus, again, patient selection is critical.[47]

The systemic inflammatory response associated with the early phase of necrotizing pancreatitis frequently results in fever and should not prompt prophylactic or empiric antibiotic usage as the infection of necrosis during this phase is rare. Routine "prophylactic" antibiotic administration to prevent infection of pancreatic necrosis is not recommended.[30,31] Antibiotics should only be prescribed as the treatment of documented infection or as empiric coverage during an infectious work-up in a patient with clinical deterioration.[2,30,31] In the early phase of necrotizing pancreatitis, mortality is predominately driven by multiple organ failure.[7,8]

Late Phase

The late phase in necrotizing pancreatitis begins a few weeks (>2 weeks) after disease onset and may last for several months, as overall disease duration is on average 5 to 6 months.[25,48–50] In the most severe cases, acute illness may persist up to or beyond 1 year. Ongoing intensive care may be required as persistent organ failure is common and present in 35% to 40%.[7,8] Attention to nutrition remains extremely important—critical illness and long-standing subacute inflammation can quickly result in nutritional

depletion. As with the early phase, enteral nutrition is preferable to total parenteral nutrition. The route of administration (nasogastric, nasojejunal, percutaneous gastrostomy, and percutaneous gastrojejunostomy) is less important and should be tailored to the individual patient, understanding the risks and benefits unique to each means of enteral access.

Several local and systemic complications may develop during the late phase. Critical illness, systemic inflammation, and infection predispose necrotizing pancreatitis patients to an increased risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) observed in 16% to 38% of patients, and pulmonary embolism (PE) documented in up to 6% of all necrotizing pancreatitis patients.[51,52] Routine chemical VTE prophylaxis should be administered to all patients without clear contraindications, and strong consideration should be given to serial 4-extremity ultrasound screening to promote early DVT detection, which allows for prompt initiation of full-dose anticoagulation and has been shown to decrease the development of symptomatic PE.[52] Splanchnic vein thrombosis is also extremely common and develops in about 50% of necrotizing pancreatitis patients.[52,53] This problem is likely due to a combination of mass effect and locoregional inflammation involving the portal, superior mesenteric, and/or splenic veins (**Fig. 6**). The ideal treatment strategy for pancreatitis-induced splanchnic vein thrombosis remains unknown. Anticoagulation may be required with thrombosis of the portal and/or superior mesenteric veins; however, anticoagulation for isolated splenic vein thrombosis is generally not warranted.[54] Left-sided (sinistral) portal hypertension may develop and can impact the selection of intervention, if warranted. Spontaneous bleeding in the setting of this sinistral portal hypertension is uncommon.[54] On the other hand, bleeding from

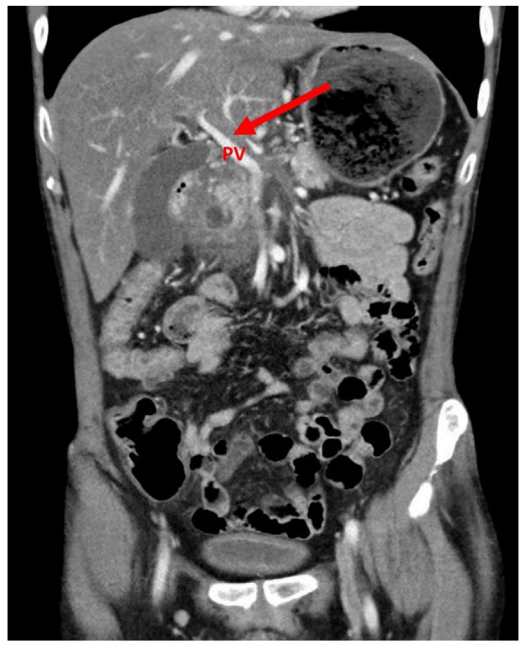

Fig. 6. Acute nonocclusive portal vein (PV) thrombosis (*arrow*) from necrotizing pancreatitis. In this case, thrombosis extended from the inferior mesenteric vein to the main PV, and into the left PV.

visceral artery pseudoaneurysms occurs in about 4% of necrotizing pancreatitis patients and may involve virtually any visceral artery.[55] Clinicians must be aware of this potentially life-threatening problem and have a low index of suspicion to obtain arterial-phase cross-sectional imaging to secure this diagnosis. Visceral artery pseudoaneurysms are best treated with urgent/emergent percutaneous angioembolization (**Fig. 7**).[55]

The impact of locoregional inflammation extends beyond vascular complications. Gastric outlet obstruction and biliary stricture can develop from regional inflammation and/or mass effect from necrosis.[46,53,56] DPDS can present with recurrent pancreatic pseudocysts, recurrent obstructive pancreatitis, and/or pancreaticocutaneous fistula and frequently requires multiple interventions to treat.[25,35,57] Furthermore, the presence of DPDS may impact decision making when necrosis intervention is needed.[25,57–59] Colonic complications, with ischemia being the most common, are associated with considerable mortality and develop in up to 11% of necrotizing pancreatitis patients.[60] Spontaneous gastrointestinal fistulae may occur or develop after necrosis intervention.[53] Fistulae involving the duodenum represent a particularly challenging problem

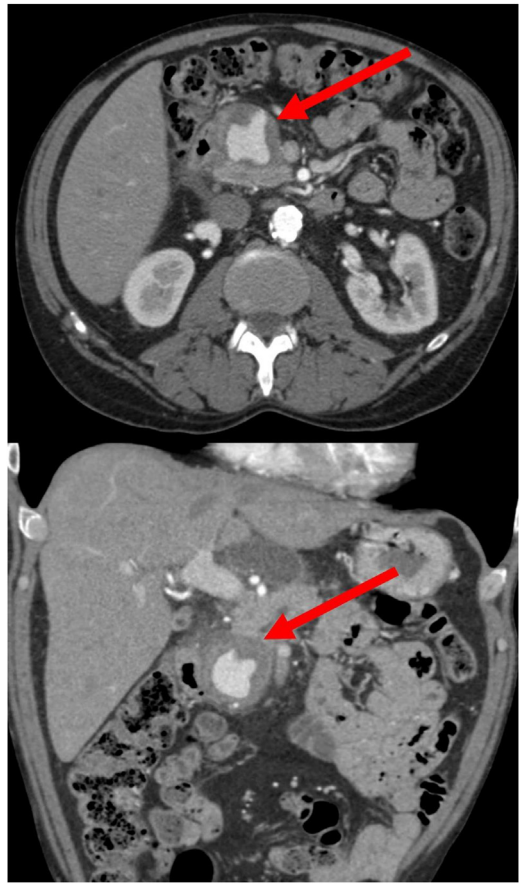

Fig. 7. Representative axial (*top*) and coronal (*bottom*) computed tomography images demonstrating visceral artery pseudoaneurysm in necrotizing pancreatitis arising from a branch of the anterior pancreaticoduodenal artery (*arrows*).

associated with significant morbidity and mortality.[46] Intra-abdominal hypertension resultant to profound systemic inflammatory response, aggressive fluid resuscitation and third-spacing, ascites formation, large-volume necrosis, and/or ileus in NP is common. Progression to abdominal compartment syndrome (ACS) is uncommon, but clinicians must be aware of this potential complication as ACS represents a life-threatening emergency with considerable morbidity and mortality.[61,62] Surgical emergencies and management strategies are discussed in subsequent sections.

Nosocomial extrapancreatic infections are extremely common in patients with necrotizing pancreatitis. In the setting of clinical concern for infection, confirmatory testing should direct the appropriate duration of antibiotics. When infection is ruled-out, empiric antibiotic therapy should be halted.[63] Tailoring empiric antibiotic therapy based on culture is critically important given the high incidence of antimicrobial resistance and *Clostridium difficile* infection.[64] Infected pancreatic necrosis develops in 20% to 40% of patients and is the primary indication for intervention in necrotizing pancreatitis (which is discussed in detail in subsequent sections).[6–8,63,65] The impact of fungal infection of pancreatic necrosis is not clear but tends to develop in patients with more severe disease, a prolonged disease course, and frequent and/or prolonged antibiotic therapy, further highlighting the importance of judicious antibiotic therapy.[66]

When patients are suitable for discharge from inpatient treatment, several outpatient goals of care must be achieved. Nutritional optimization and physical rehabilitation should be continued to promote recovery and return to baseline. Communication between the patient, the patient's outpatient care team, and the responsible pancreatologist must be readily available to monitor clinical improvement, allow for early detection of developing complications, and minimize hospital readmission.[44] Unplanned hospital readmission is extremely common in this patient population, and the tenets of frequent communication and early detection of impending treatable problems decrease the need for hospital readmission.[6,44] Additionally, reprieve from inpatient treatment can decrease the risk of nosocomial infection and exposure to multi-drug resistant organisms. Finally, routine, short-interval follow-up should be scheduled to evaluate progress and plan for appropriate intervention, if required.

INTERVENTION IN NECROTIZING PANCREATITIS

Evolution in Treating Necrotizing Pancreatitis

Pancreatic and peripancreatic necrosis was traditionally treated by operative surgical debridement, a strategy that often included multiple debridements and in some cases laparostomy to facilitate planned reoperations.[67,68] Historical reports of operative pancreatic debridement were associated with high perioperative morbidity—including enteral and pancreatic fistula—as well as high postoperative mortality rates, often in the 25% to 40% range.[69,70] With improved understanding of the disease process and accumulated operative experience, mortality after pancreatic debridement has decreased substantially over time.[49,71]

The past 20 years have witnessed a remarkable change in the treatment of pancreatic necrosis.[9,72] With application of contemporary "step-up" strategies, most patients are managed successfully using minimally invasive treatment approaches including percutaneous therapy, endoscopic directed therapy, and often some combination of the 2.[48,50,65,72–75]

Indications and Goals of Intervention

The principles of intervention to address pancreatic necrosis are (1) to control infection, (2) evacuate fluid and solid necrotic debris, (3) drain pancreatic fistula (typically

the result of DPDS) either internally or externally, (4) prevent recurrent pancreatitis (by cholecystectomy in the setting of biliary pancreatitis), and (5) establish enteral access. It is ideal to accomplish these goals with minimal physiologic disruption in a uniformly frail patient population. A "one-size-fits-all" approach does not apply in necrotizing pancreatitis—a fundamental general principle is that one single debridement technique does not apply widely to all patients. Care of the necrotizing pancreatitis patient requires a dedicated physician to lead a multi-disciplinary team providing closely monitored care during this long-term acute/subacute illness. Selection of type and timing of intervention requires expert clinical judgment; the ideal treatment approach is individualized to the patient's unique clinical circumstance and depends highly on local experience and expertise.

Additional important selection considerations include the patient physiology: no necrotizing pancreatitis patient is ever physiologically "perfect" for intervention. Residual necrosis is a catabolic situation and good judgment is required to identify the appropriate window for intervention. This point speaks to the need to have at least one physician involved in a patient's care longitudinally to evaluate changes in progress. Necrosis distribution plays perhaps an equally important role in decision making. A patient with necrosis consolidated in the lesser sac with or without (usually with) a disconnected pancreatic tail is ideally suited for a transgastric approach (either endoscopic or surgical) (**Fig. 8**, left), while a patient with necrosis tracking down one paracolic gutter may be approached with percutaneous drainage with aggressive drain management (frequent drain exchanges/repositioning or additional drain placement) followed by video-assisted retroperitoneal debridement (VARD), if necessary (see

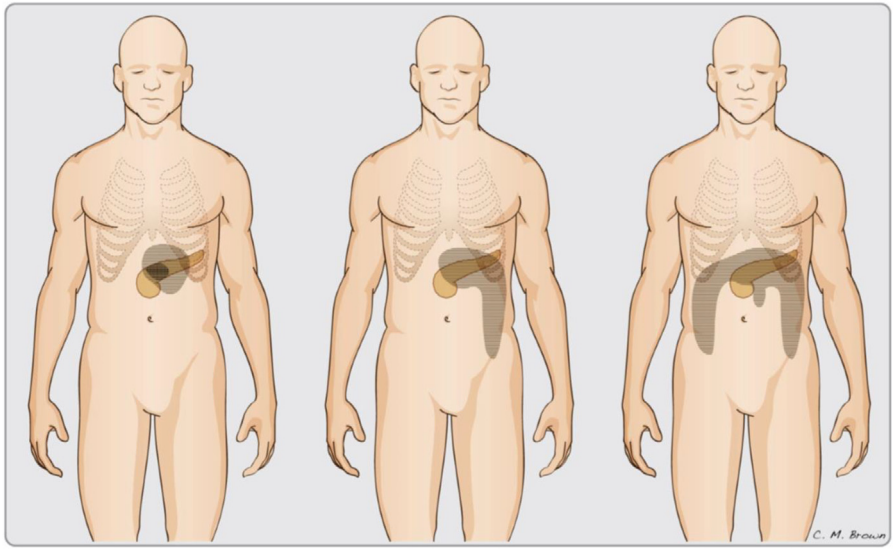

Fig. 8. Patterns of necrosis in necrotizing pancreatitis. Necrosis confined to the lesser sac (*left*) may be best ideal for a transgastric approach, either endoscopic or surgical. Patients with necrosis tracking down one paracolic gutter (*middle*) are suitable for percutaneous drainage and subsequent videoscopic-assisted retroperitoneal debridement (VARD), if needed. Multiple fields of retroperitoneal necrosis (*right*) may be best served with operative pancreatic debridement. (Illustration reprinted from "Transgastric Pancreatic Necrosectomy: How I Do It" by Zyromski et al (2016).[88])

Fig. 8, middle). A patient with multiple retroperitoneal fields involved with necrosis may be best served with operative debridement as a first treatment step (see Fig. 8, right).

Natural History of Pancreatic Necrosis

Fig. 9 illustrates the natural history of pancreatic and peripancreatic necrosis. A small proportion of necrotizing pancreatitis patients will resolve their necrosis without any specific intervention. This is approximately 5% to 10% in large series, but may be as high as 20% in select populations.[9,53] A second group of patients will develop infected necrosis, documented either by cross-sectional imaging with gas bubbles or by directly sampling and culturing the necrosis. A third group of patients will have persistent necrosis, which if asymptomatic may be observed. Patients with persistent sterile necrosis may develop unremitting symptoms without resolution over time, including gastric outlet obstruction, abdominal pain, or "persistent unwellness." These patients with symptomatic (presumed sterile) necrosis should be considered for debridement. Notably, in patients with presumed sterile necrosis a significant percentage (up to 40%) will be found to have occult infection.[76] Infected necrosis rarely resolves with antibiotic therapy alone and is the most common indication for intervention in necrotizing pancreatitis. Infected necrosis develops in 50% to 60% of patients, and the subsequent clinical course is extremely heterogeneous.[6–8,53] Treatment may require few interventions over the course of weeks to months; on the other hand, repeated intervention over months to years is not uncommon.

Percutaneous Drainage

Percutaneous drainage has become the first mechanical interventional step in the "step-up" approach for most patients with necrotizing pancreatitis, as most institutions have the resources to perform percutaneous drainage safely. It was observed in the PANTER trial that nearly one-third of patients resolved their pancreatic/peripancreatic collections with percutaneous drainage alone.[72] This finding has been validated in subsequent studies, although no published data exist to identify accurate predictors of success or failure of percutaneous drainage alone.[25,48,77] Once treatment begins by any approach—percutaneous, endoscopic, or otherwise—the clock is ticking, and efforts should be directed toward evacuating the infected solid necrosis expediently. Most institutions favor a strategy of fairly short (3–5 day) interval imaging with frequent upsizing or repositioning of percutaneous drains or placement of additional drains.[25,78] While labor intensive, this aggressive approach to percutaneous

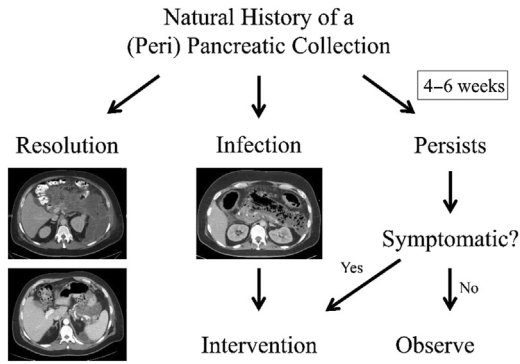

Fig. 9. Natural history of pancreatic and peripancreatic necrosis.

drainage of pancreatic necrosis effectively evacuates residual necrosis, minimizes recurrent bouts of sepsis from undrained infected necrosis, and accelerates recovery. In patients with infected necrosis, this aggressive and proactive approach to drain care has been associated with an increased likelihood of successful necrosis evacuation with percutaneous drainage alone and may reduce the likelihood of surgical debridement.[25,78] Percutaneous drains by themselves will not provide definitive treatment in two-thirds of patients with pancreas necrosis, and clinical judgment is critically important once treatment has begun. In the situation where treatment by percutaneous drainage stalls, the next step in the approach may include endoscopic "dual-modality drainage," sinus tract endoscopy, or operative surgical debridement. Prior to initial drain placement, multi-disciplinary evaluation should include thoughtful discussion on options to "step-up" to VARD. To allow for VARD, the optimal initial percutaneous drain placement is via a left-sided retroperitoneal approach with a minimum drain size of 12 to 14 French.[72,79] Percutaneous access should be placed low in the necrosis field with the drain positioned through the necrosis in the straightest possible pathway. This allows access to left retroperitoneal necrosis as well as necrosis adjacent to the pancreatic neck, body, and tail. Right-sided VARD is feasible to address necrosis in the right retroperitoneum but may limit access to necrosis directly adjacent to the pancreas.

Predicting success of percutaneous drainage alone in definitively managing pancreatic necrosis is challenging, but one-third of patients will be successfully treated with percutaneous therapies.[25,72,78] Several studies have attempted to further elucidate predictors of success/failure of percutaneous drainage, but further investigation is warranted. One study identified male sex, multiple organ failure, increasing volume of necrosis, and heterogeneity of necrosis as negative predictors of success.[80] Not surprisingly, clinical and radiographic improvements after placement of percutaneous drains have been identified as positive predictors of success.[81] Finally, patients with DPD are more likely to require "step-up" to endoscopic and/or operative debridement of necrosis.[25]

Transgastric Debridement

Endoscopic transgastric debridement was first described in 1996 and over the next 2 decades, sporadic small case reports emerged in both the medical and surgical literature.[82] More recently, enthusiasm has grown significantly for endoscopic transgastric debridement, and many institutions with advanced endoscopic experience utilize an "endoscopic step-up approach" as initial intervention in necrotizing pancreatitis. Patients with necrosis confined to the lesser sac are ideal candidates; however, with accumulating experience, aggressive endoscopists have pushed the envelope in terms of which necrosis morphology to approach endoscopically.[83,84] An important consideration is the available local expertise—even in the most skilled hands, endoscopic evacuation of peripancreatic necrosis requires multiple debridement sessions, each under a general anesthetic. Patient selection is critical and still becoming better delineated but may be best suited for patients with nonbiliary etiology of pancreatitis. In patient's suitable for endoscopic drainage/debridement, the endoscopic step-up approach was associated with similar mortality rates when compared with surgery.[85,86] Composite endpoints favor an endoscopic step-up approach, when suitable, owing to decreased rates of pancreatico-cutaneous fistula and decreased systemic inflammatory response.[85,86] The long-term success of endoscopic debridement in patients with DPDS is incompletely delineated, but appears to be durable in most patients (~70%), with about 30% of patients treated surgically for recurrent symptoms from DPDS after endoscopic transgastric debridement.[59]

Surgical transgastric debridement provides the ability to address pancreatic necrosis as well as perform cholecystectomy with cholangiography in the same setting. Several surgical groups have reported excellent results with increasingly larger series of transgastric debridement.[59,87] The authors' opinion is that surgical transgastric debridement should be the treatment of choice with patients with biliary pancreatitis and appropriate necrosis morphology.[88] This approach may be ideal for patients with DPDS, as the transgastric approach drains the disconnected tail into the stomach. These patients experience recurrent pancreatitis and fluid collections approximately 20% of the time and should be counseled accordingly.[59]

Minimally invasive surgical (MIS) approaches include video-assisted retroperitoneal debridement (VARD) as well as sinus tract endoscopy/necrosectomy. VARD was studied prospectively by the Dutch group in the PANTER trial.[72] A small incision permits insertion of an operating nephroscope or video endoscope to guide debridement. This approach may be performed by left or right flank; occasionally, bilateral VARD are used to treat extensive necrosis. Sinus tract necrosectomy involves a similar technical approach and uses endoscopy to guide debridement through a small incision; however, this approach is typically carried out along established drain tracts in a trans-peritoneal orientation.

A fundamental principle of either retroperitoneal or trans-peritoneal minimally invasive approach is allowing an appropriate period of time for the necrosis cavity to mature. This "window" permits adequate debridement with minimal disruption of surrounding tissue.

Open Pancreatic Debridement

Open pancreatic debridement has traditionally served as the gold standard for the evacuation of infected or symptomatic solid necrosis. No contemporary minimally invasive approach has ever been compared with open debridement in a randomized fashion; this comparison in current time is not practical. Open pancreatic debridement provides the advantage of addressing multiple necrosis fields, biliary pathology, and potentially a small pancreatic tail remnant in a single procedure. The safety of this procedure is established, and in experienced hands mortality is less than 2%.[49,71,89] Safety is a particularly important consideration in the setting of superior mesenteric or splenic vein thrombosis. In this circumstance, resultant gastric varices may lead to major hemorrhage during transgastric approaches. Open pancreatic necrosectomy is time tested and widely applicable to a well-trained surgeon familiar with based surgical principles. In current times, open pancreatic debridement is often relegated to the last effort when other percutaneous and endoscopic approaches have unsuccessfully resolved pancreatic necrosis.[49,89]

From a technical standpoint, it is important to review recent cross-sectional imaging to understand the pattern of residual necrosis distribution. Intraoperative ultrasound is useful to localize collections. Adhesions from the small bowel to the underside of the transverse colon are quite common. Safe approach to necrosis is obtained via lateral paracolic gutters. Perhaps the most effective debridement tool is the "educated finger" of the surgeon. A ring forceps works well too; however, only freely mobile necrosis should be debrided. Large caliber closed suction drains are placed in the necrosis bed after vigorous irrigation. Gastrojejunostomy feeding tubes facilitate postoperative management as many patients have gastric ileus (may vent gastrostomy port) but will tolerate small bowel feeding.[47]

Contemporary series of pancreatic debridement in experienced hands document excellent outcomes. To reiterate, judgment regarding the timing of operation and

the extent of operation is critically important. In some circumstances, "damage control" debridement may be necessary.[89]

In summary, important considerations in necrotizing pancreatitis intervention include the etiology of pancreatitis, necrosis distribution (including percentage of solid necrosis), parenchymal involvement, the presence of DPDS, splanchnic vein thrombosis, infection, patient physiology, and local expertise. One size technique does not fit all patients. A dedicated physician taking "ownership" of patient care is required ideally to promote interface among a multi-disciplinary team through the duration of this long-term acute illness.

Surgical Emergencies in Necrotizing Pancreatitis

Several clinical situations may warrant emergent surgical intervention in NP including gastrointestinal perforation or ischemia, ACS, or life-threatening hemorrhage not amenable to percutaneous angioembolization. Broadly speaking, surgical emergencies should aim to address the emergent pathology, with minimal to no debridement of (peri)pancreatic necrosis. Gastrointestinal perforation or ischemia is associated with high rates of morbidity and mortality.[46,60] General surgical principles may be applied to resection and/or repair. In the setting of gastroduodenal ischemia or perforation, gastrojejunostomy feeding tube is recommended, if feasible. Colonic ischemia or perforation warrants resection and fecal diversion with ileostomy/colostomy. With ischemia or perforation of the proximal small bowel, careful consideration should weigh the risks/benefits of enteroenterostomy (anastomotic leak) with proximal diversion (high-output ostomy with associated malabsorption and fluid loss). In patients with ACS, decompressive laparotomy should be considered a means of last resort. Principles in treating intra-abdominal hypertension aiming to prevent progression to ACS should be applied to patients with necrotizing pancreatitis.[90] In the event, decompressive laparotomy is required as a life-saving maneuver, drainage/debridement of necrosis should not be attempted, but rather deferred for a later date (a "live to fight another day" approach). Visceral artery pseudoaneurysm is optimally treated with percutaneous angioembolization and is rarely refractory to this approach with technical success rates exceeding 95%.[55] With bleeding refractory to percutaneous angioembolization, surgical control of hemorrhage may be required. In low-volume centers, laparotomy with abdominal packing may be a temporizing measure to allow transfer to a hepato-pancreato-biliary center. In greater than 90% of cases, visceral artery pseudoaneurysm affects arterial branches that may be surgically ligated with minimal consequence (splenic artery—36%, gastroduodenal artery—24%, gastric/gastroepiploic arteries—18%, pancreaticoduodenal arcade—12%).[55]

TIMING OF CHOLECYSTECTOMY

Cholecystectomy in patients with mild gallstone pancreatitis should be performed during the same hospital admission to reduce the risk of recurrent gallstone-related complications, but concern has existed that early cholecystectomy may increase the risk of technical complications.[30,91] Strong evidence from the PONCHO trial showed that an early cholecystectomy (before discharge) effectively reduces the rate of recurrent gallstone-related complications compared with interval cholecystectomy.[92]

The timing of cholecystectomy in severe pancreatitis is more complex. Historically, cholecystectomy was delayed until the need for intervention on necrosis declared itself.[93] In the contemporary era of minimally invasive endoscopic, percutaneous, or MIS, surgical necrosectomy timing of cholecystectomy is less well defined. Retrospective data show that more than 20% of biliary pancreatitis patients treated with

the step-up approach developed biliary complications during the wait for cholecystectomy.[94] A more recent prospective report shows that beyond 10 weeks, the incidence of biliary complications will increase.[95] Therefore, performing cholecystectomy within 10 weeks from onset of AP—when possible based on the clinical disease features—should be strongly encouraged.

OUTCOMES INCLUDING LONG-TERM SEQUELAE

The modern mortality in all necrotizing pancreatitis patients is about 10% to 15%.[6–9] Mortality rates are higher in patients with organ failure, those with infected necrosis, or those who require intervention, ranging from 10% to 30%.[7,8,48,65,71,72,96] Organ failure and infected necrosis are the 2 strongest influencing factors associated with mortality.[7,8] Patients who survive an episode of acute necrotizing pancreatitis generally required about 5 to 6 months for acute/subacute disease resolution.[44,49,53,59] Emerging research has identified a variety of long-term disease sequelae in necrotizing pancreatitis survivors (**Table 2**).[53]

Pancreatic endocrine and exocrine insufficiency after acute pancreatitis are common; the risk of pancreatic function loss is directly correlated with the disease severity and volume of parenchymal necrosis.[53,97–99] In patients with necrotizing pancreatitis, endocrine (type 3c diabetes mellitus) and exocrine insufficiency develop in 40% to 60% and 10% to 40% of survivors, respectively.[53,77,98–100] In a long-term follow-up, the development of pancreatic endocrine and exocrine insufficiency was not dependent on intervention type, be it percutaneous, endoscopic, surgical, or a combination.[53] Five-year follow-up of a randomized controlled trial comparing endoscopic

Table 2
Long-term sequelae of necrotizing pancreatitis

Long-Term Sequelae	*Incidence*
Endocrine insufficiency	40%–60%
Exocrine insufficiency	10%–40%
Splanchnic vein thrombosis	50%
Disconnected pancreatic duct syndrome	45%
Recurrent acute pancreatitis	20%
Chronic pancreatitis	10%–20%
Biliary stricture	16%
Duodenal stricture	5%
Uncommon Sequelae	
Tracheal stenosis	
Ureteral stricture	
Colonic stricture	
Progressive renal failure	
Pancreatic ductal adenocarcinoma	
Gastrointestinal failure requiring transplant	
Male impotence	
Metabolic peripheral polyneuropathy	
Pericardial effusion	
Deafness	
Blindness	

and surgical step-up approaches demonstrated no difference between groups in rates of pancreatic endocrine or exocrine insufficiency.[101] Additionally, reintervention rates were lower in the endoscopy group during the long-term follow-up.

One in 5 patients (20%) may experience recurrent acute pancreatitis during long-term follow-up and chronic pancreatitis is reported to develop in 10% to 20%.[53,77,101,102] Pancreatic duct stricture after necrotizing pancreatitis contributes to the development of recurrent acute pancreatitis and chronic pancreatitis.[53,103,104]

Several less commonly reported complications are noteworthy. Splanchnic vein thrombosis develops in up to 50% of patients, with infrequent recanalization.[51,53,104,105] This situation often results in either left-sided or generalized portal hypertension. DPDS is an increasingly recognized complication of necrotizing pancreatitis. DPDS is diagnosed in 45% of patients and commonly manifests itself after acute disease resolution.[25,35,53] The treatment of DPDS and its associated recurrent pancreatitis and/or pseudocyst frequently require endoscopic and/or surgical intervention. Biliary stricture and duodenal stricture may form as a result of the local inflammatory process in necrotizing pancreatitis and frequently require interventional therapy.[46,56] Gastric, duodenal, enteric, and colonic fistulae may develop during necrotizing pancreatitis or as a result of its treatment; these fistulae often persist after disease resolution.[53,60] Incisional hernia is more common in patients requiring laparotomy for necrotizing pancreatitis when compared with laparotomy for other indications.[53,106] Rare complications from necrotizing pancreatitis or its treatment that are reported as case reports or as anecdotes range from tracheal stenosis, ureteral stricture, colonic stricture, progressive renal failure, pancreatic ductal adenocarcinoma, irreversible gastrointestinal failure requiring multivisceral transplant, male impotence, metabolic peripheral polyneuropathy, pericardial effusion, deafness, and blindness.[53]

Clinicians should be aware as necrotizing pancreatitis has a significant impact on patient's mental health both during the acute phase and long-term after disease resolution. The disease elicits post-traumatic stress disorder, anxiety, and depression. Several studies have evaluated a variety of quality of life metrics after acute necrotizing pancreatitis resolution, and the theme is a long-term impairment in quality of life regardless of treatment strategy; though, the exact impact remains difficult to quantify.[100,101,107–109] Studies evaluating long-term follow-up establish that quality of life is not dependent on the type of necrosis intervention but rather successful evacuation of necrosis and recovery from acute illness. Of significance, these studies report that during follow-up 40% to 75% of patients reported disability that prevented return to baseline, pre-necrotizing pancreatitis function. Clearly, long-term follow-up of necrotizing pancreatitis survivors is important.

After acute disease resolution, routine follow-up should include focused history, physical examination, and laboratory screening for the development of these long-term sequelae in survivors of necrotizing pancreatitis.

SUMMARY

The past 2 decades have witnessed considerable evolution in our understanding of both the disease process and technical approaches to managing pancreatic necrosis. Patients requiring interventions should uniformly be treated by the step-up approach. This approach starts with antibiotics, stepping up to percutaneous drainage or endoscopic therapy and progressing to surgical therapy. A combination of these approaches is often necessary to expedite disease resolution. Objective metrics in determining the optimal timing for step-up are needed. It is unknown which subset of patients may benefit from operative pancreatic debridement as first-line therapy.

An unmet need is the investigation, discovery, and development of therapy directed toward treating the disease itself, as current therapy simply addresses complications of the disease.

CLINICS CARE POINTS

- Clinical care in nerotizing pancreatitis initially focuses on supportive care - symptom control, adequate nutrition, support of organ failure, and prevention of infection.
- Necrosis intervention is indicated in infected necrosis or symptomatic necrosis with persistent unwellness.
- A variety of approaches to necrosis intervention exist - selection should be tailored to the individual patient with multidisciplinary input.
- Patients surviving necrotizing pancreatitis benefit from long-term follow-up as late complications are common.

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