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Management of Infected Pancreatic Necroses: An Endoscopic Approach

Eduardo Rodrigues-Pinto[1,2] *and Todd H. Baron*[1]

[1] *Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC, USA*
[2] *Gastroenterology Department, Centro Hospitalar São João, Porto, Portugal*

Pancreatic Necrosis

Pancreatic fluid collections (PFC) can occur as a complication of acute pancreatic injury (acute pancreatitis, trauma, surgical resection, or injury to the pancreas during abdominal surgery) or chronic injury (chronic pancreatitis, autoimmune pancreatitis). At the basis of this pancreatic injury is disruption of the main pancreatic duct and/or side branches. Acute necrotizing pancreatitis is at the severe end of a spectrum of inflammation associated with pancreatitis, resulting in cell death. Pancreatic necrosis is defined as nonviable pancreatic parenchyma usually with associated peripancreatic fat necrosis. It is reported by some to occur in approximately 15–20% of all episodes of pancreatitis [1]. The resultant devitalized tissue becomes a potential bed for infection. Approximately 30% of patients with pancreatic necrosis develop infection [2,3]. The amount of necrotic tissue is the strongest predictor of mortality in necrotic pancreatitis. Fortunately, with early recognition and improvements in critical care most patients survive the early phase of systemic inflammatory response syndrome and many survive multisystem organ failure.

In the acute period, pancreatic necrosis can be an acute necrotic collection in which there is a variable amount of fluid and necrosis [4]. It is detected radiographically on contrast-enhanced computed tomography (CT) by the presence of nonenhancing pancreatic parenchyma. By around 4 weeks after onset the collection continues to evolve and may expand the initial area of necrosis. Such collections contain both liquid and solid debris and are referred to as walled-off necrosis (WON) or walled-off pancreatic necrosis (WOPN), in which the collection is defined by a fibrotic and inflammatory wall. The term infected necrosis refers to bacterial invasion of necrotic pancreatic tissue and can lead to clinical infection, and sepsis and death. Infected necrosis is rare during the first week [5,6]. Most of the evidence suggests no absolute correlation between the extent of necrosis and the risk of infection and duration of symptoms [2,5]. The mortality rate approaches 100% if intervention and drainage are not undertaken for infected necrosis. Even with aggressive intravenous fluid replacement, nutritional support, and early intervention of pancreatic necrosis, the presence of pancreatic necrosis is associated with an overall increase in mortality. The mortality rate from sterile pancreatic necrosis is 10% and rises to 30% when infected [7]

Mechanical Intervention

Mechanical intervention for pancreatic necrosis can take the form of surgical, percutaneous, and endoscopic debridement. Open surgical therapy is no longer considered the gold standard [8] and has been replaced by minimally invasive approaches [9,10] using flexible endoscopic, and rigid endoscopic [11], percutaneous and laparoscopic approaches, alone or in combination [6]. It has been almost 20 years since the first report of endoscopic drainage of pancreatic necrosis [12]. Optimal management of necrotizing pancreatitis requires a multidisciplinary team including dedicated surgeons, interventional radiologists, and gastrointestinal endoscopists. Such a multidisciplinary team needs to be involved from the onset of the disease to decide if, when, and how an intervention needs to be performed.

Recent guidelines state that there is no need for intervention in asymptomatic patients with sterile necrosis,

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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regardless of its size, location, and extension [13,14]. In the vast majority of patients, the necrosis will resolve spontaneously. An intervention for sterile pancreatic collections is only indicated in patients with persistent gastric outlet, intestinal, or biliary obstruction due to mass effect of WOPN at least 4–8 weeks after onset of symptoms. In case of persistent symptoms such as pain and "failure to thrive" intervention is more debated and current guidelines suggest that in such cases, intervention can be considered 8 weeks after onset [14]. In case of infected, but minimally symptomatic necrosis, it is advisable to delay any surgical, radiologic, or endoscopic approach for more than 4 weeks in order to facilitate the formation of WOPN with liquefaction of the contents. Infected necrosis with clinical instability requires immediate drainage in order to avoid fatal complications. In these cases, minimally invasive methods of necrosectomy should be preferred to open surgery. The distinction of sterile from infected necrosis is difficult but very important as it greatly affects prognosis and management. Routine percutaneous fine-needle aspiration (FNA) of pancreatic and peripancreatic collections for the detection of infection should not be routinely performed. It may postpone interventions, give false negative results, or induce secondary infection [6]. Suspicion of infection is usually based on clinical deterioration despite medical support, high fever with rising inflammatory markers, and/or positive blood cultures. The presence of gas on imaging studies is highly suggestive of infection, likely due to fistula, but it is only present in a minority of cases [15,16]. Infection can be confirmed by FNA or through cultures obtained at the time of drainage, and can be used to guide antibiotic therapy [13,14].

The goals of endoscopic therapy for infected WOPN are (i) drainage of fluid and removal of solid components using a transmural approach (transgastric or transduodenal) and (ii) treatment of pancreatic ductal leaks and/or disruptions using a transpapillary approach, in selected patients. Theoretically, addressing pancreatic disruptions may lead to better long-term outcomes [17]. Transpapillary endoscopic drainage as primary therapy of WOPN is not an adequate method to remove solid debris. Removal of solid debris is vital to any type of intervention during transmural drainage, which can be "mechanical," by irrigation, or a combination.

Endoscopic access is best performed when the wall is mature, usually 4 weeks or more after the episode of pancreatitis. This period of time between onset of the disease and intervention is suggested to be associated with lower mortality and intervention is delayed if the clinical condition allows [2]. As necrotic collections become organized into WOPN, they are more amenable to intervention. In case of proven or suspected infected necrotizing pancreatitis, intervention should be delayed where possible until at least 4 weeks after initial presentation [2,14]. An endoscopic transgastric access can be created even as early as 2–3 weeks after the onset of acute pancreatitis in the setting of sepsis and acute necrotic collection as long as they are organized as determined by CT or magnetic resonance imaging.

Transmural Drainage

The evolution of endoscopic therapy of WOPN began with pseudocysts drainage using small-diameter transmural tracts (8 mm), placement of 10Fr stents and a nasocystic irrigation tube [12]. Early in the endoscopic experience many patients required adjunctive percutaneous drains, especially to treat large paracolic gutter extensions [18]. In patients who were intolerant to nasocystic irrigation tubes and/or in whom it was anticipated that irrigation may be required for many weeks, an alternative to nasocystic lavage was the placement of a percutaneous endoscopic gastrostomy tube (PEG) with placement of a "jejunal" extension tube into the collection [19]. Larger diameter transmural dilations were then added to the irrigation approach. Nasocystic irrigation tubes can be used for continuous flushing with sterile fluid per 24 hours or lavaged every 3–4 hours for several days to weeks depending on the amount of debris present and patient tolerance and may avoid the need for subsequent necrosectomy [20]. However, they are uncomfortable, and with the advent of large-diameter transluminal metal stents, their use is not mandatory. Such nasocystic irrigation tubes are no longer routinely placed [21].

Direct endoscopic necrosectomy (DEN) was introduced by Siefert et al. [22], and subsequently Seewald et al. [23], as a method to remove necrotic tissue by passing forward- or side-viewing endoscopes transmurally into the collection; baskets, grasping forceps, and snares are used to remove solid debris [20,24]. Transmural placement of large-diameter covered (esophageal) self-expandable metal stents (SEMS) [25,26] or 15 mm lumen self-expandable lumen-apposing metal stents can facilitate necrosectomy and avoid the need for repeated balloon dilation of the gastric or duodenal wall (Figs 30.1, 30.2, and 30.3) [24]. Hydrogen peroxide may facilitate the removal of necrotic debris during DEN and reduce the likelihood of further necrosectomies [27].

In conjunction with interventional radiology, several hybrid approaches have also been described [28]. In some patients with peripheral collections that are not accessible from a transluminal approach, a percutaneous

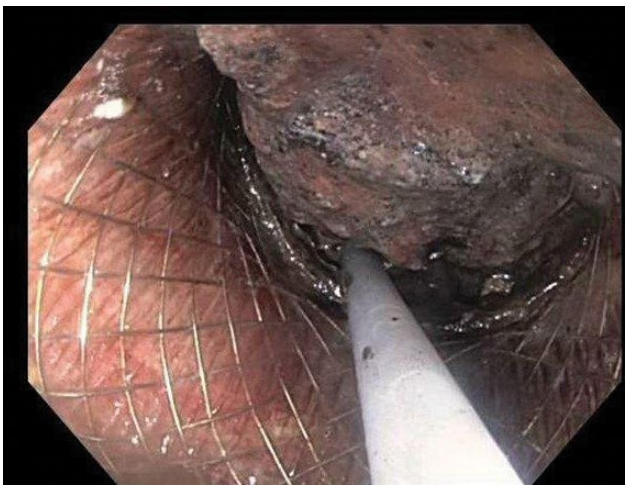

Figure 30.1 Endoscopic view of pancreatic necrosis. The endoscope is positioned just in front of a recently deployed fully covered self-expandable 15 mm luminal apposition stent. A snare is being used to evacuate solid debris.

Figure 30.2 Necrotic debris evacuated from the patient presented in Fig. 30.1.

drain is placed. Subsequently, a large-bore SEMS is placed through the percutaneous tract to allow for DEN with a flexible endoscope.

Gluck and colleagues at the Virginia Mason Medical Center in Seattle, Washington, USA described a dual-modality drainage technique. CT-guided percutaneous irrigation/drainage catheter placement is followed by endoscopic transmural drainage. The percutaneous catheter is used for irrigation, with egress internally. This allows avoidance of DEN. In their institution this approach resulted in decreased length of hospitalization and number of radiologic and endoscopic procedures compared with either modality alone [29]. This method

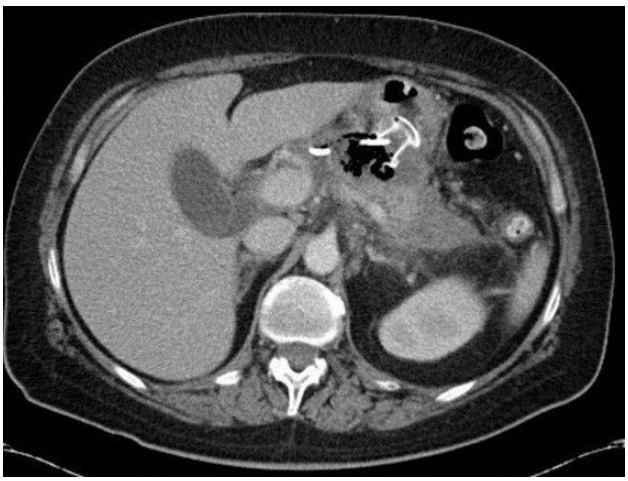

Figure 30.3 CT scan from the patient shown in Figs 30.1 and 30.2 shows the expandable stent in place and near resolution of necrotic cavity.

of treatment was reported to be superior to a strictly percutaneous approach, not only in speeding resolution, but also in precluding the development of external fistulas [26] and bleeding.

For complex organized necrosis, Varadarajulu and colleagues described an endoscopic ultrasound (EUS)-guided multi-gateway approach [30], which utilizes two or more transmural entry approaches to permit irrigation, aiming to improve drainage of the often multiseptated necrotic collections. Nasocystic irrigation enters one site and egresses from another. Following the procedure, 200 mL of saline is irrigated every 4 hours through the nasocystic tube, shifting patient position between flushes.

Transmural Entry Devices

Devices used to perform transmural puncture of WOPN can be divided into cautery and noncautery devices. Cautery devices include standard diathermy wires (needle knifes), specialized fistulotomy devices (cystotome, CST-10, Cook Endoscopy, Winston-Salem, NC, USA) and specialized stent delivery systems with cautery incorporated (AXIOS EC, Boston Scientific, Marlborough, MA, USA). Noncautery devices include 19-gauge EUS-FNA needles and other miscellaneous aspiration needles (Marco-Haber variceal injector needle MHI-21, Cook Medical).

Most often the collection is punctured transmurally using EUS guidance. Fluid is aspirated to confirm entry and is sent for fluid analysis including Gram stain and culture. Correct positioning during entry can also be confirmed by contrast injection into the collection under fluoroscopy.

Stent Placement

Plastic stents are not ideally suited to drain WOPN. Recently, the use of fully covered SEMS [31] are used instead. Specially designed biflanged short stents (Axios, Boston Scientific), either with or without electrocautery-incorporated delivery systems, seem to have a high technical and clinical success rates. Due to its ease of use, such devices have simplified and streamlined EUS-guided management of PFC, particularly for endoscopic debridement of WOPN. These devices have also promoted more widespread adoption of transmural drainage as an alternative to surgery [32,33].

If a noncautery device is used to enter into the collection, the transmural tract must then be traversed (over a 0.025–0.035″ guidewire) either with a biliary dilating balloon (4 mm diameter to allow passage of the delivery system) or with a 10 F cystotome; the metal stent is then deployed. When the recently commercially available electrocautery-tipped SEMS delivery system is used, the procedure is done in a single step (puncture and stent deployment). Particular care should be taken with regard to proper device deployment, particularly the final, crucial step involving proximal flange release. According to the manufacturer's instructions, the endoscope should be pulled back slightly in order to directly visualize 2–3 mm of the black catheter shaft marker in the gastrointestinal tract before deploying the proximal flange. An alternative option that does not sacrifice a stable scope position or risk placing excessive traction on the SEMS involves releasing the proximal flange while it is still inside the endoscope, and the endoscope tip remains close to the puncture site. At that point, advancing the delivery system while gently withdrawing the endoscope allows the proximal flare to spring open as the stent exits the endoscope. However, even with electrocautery-tipped SEMS delivery systems, it is important to secure an ample length of guidewire into the collection with at least one complete loop of wire. A double pigtail stent placed through or alongside the metal stent lumen may help to prevent migration and occlusion due to impaction of necrotic material [34,35].

Anticoagulant or antiplatelets drugs should preferably be discontinued prior to transmural drainage, and certainly prior to necrosectomy. In case of severe bleeding during the procedure which cannot be treated endoscopically, immediate assistance of an interventional radiologist should be requested. Endoscopic drainage and necrosectomy are preferably performed with patients under deep sedation or general anesthesia. DEN should be routinely performed using a forward-viewing endoscope at the time of the first endoscopic procedure; schedule debridements should be performed with the interval ranging from days to weeks depending upon the inpatient or outpatient status, anticipated volume of residual necrosis, and follow-up CT. Internal drains are endoscopically removed several weeks after complete resolution of the collection and removal of external drains (if placed). Patients with infected necrosis continue antibiotic therapy, either empirically or based upon culture data obtained during drainage and/or debridement. All procedures should be performed with carbon dioxide (CO_2) insufflation since fatal gas embolism has been described.

Results of Endoscopic Therapy of Pancreatic Necrosis

There are increasing series showing that endoscopic treatment of WOPN is successful in achieving nonsurgical resolution in the majority of patients [34]. Retrospective studies have shown a treatment success rate of 45–63% for endoscopic drainage [17,20]. In a review of 10 series on endoscopic necrosectomy, the overall treatment success was 76%, mortality 5%, and procedure-related morbidity 27% [36]. Minimally invasive techniques were evaluated by a randomized trial [2,6], which showed lower morbidity rates, faster recoveries and shorter hospital stays. Evidence in favor of endotherapy is supported by others [34]. A recent systematic review considered DEN a safe (mortality rate of 6% and complication rate of 36%) and effective minimally invasive treatment (80% treatment success) in infected necrosis [37]. However, most of the studies included did not report on the most relevant parameters of disease severity or outcome measures. Guidelines now advocate that if an intervention is indicated in patients with infected necrosis, initial treatment should consist of either image-guided percutaneous catheter drainage or endoscopic transluminal drainage [14].

Adverse Events of Endoscopic Therapy of Pancreatic Necrosis

Life-threatening adverse events may arise following attempted endoscopic drainage of pancreatic necrosis. It is recommended that endoscopic drainage is performed with the availability of surgical and interventional radiology support. The most feared adverse events of transmural drainage are bleeding and perforation. Bleeding after transmural drainage may be managed supportively, endoscopically, surgically, or with angiographic embolization. If perforation occurs during attempted transgastric drainage and is limited to the gastric wall (does not involve the collection), it may be

successfully managed nonsurgically if a stent is not mistakenly placed through the perforation and outside the gastric wall. If egress of gastric contents is prevented, the gastric wall rapidly closes with conservative treatment consisting of nasogastric suction and antibiotics. Large-diameter (esophageal) SEMS can be used to close perforations [38] and in some cases tamponade bleeding. Infectious adverse events usually occur from inadequate drainage of fluid and/or solid debris. Stent migration into the collection through the gastric or duodenal wall may occur during or after endoscopic stent placement. Endoscopic retrieval is possible if the collection has not completely collapsed and the transmural tract is still patent. Fatal air embolism has been reported following DEN [39]. This has prompted the use of CO_2 rather than air insufflation during drainage.

Endoscopic therapy may be associated with adverse events and/or failures that require surgical management. It is possible that the outcome of surgical therapy may be adversely altered when compared to those patients undergoing primary surgical therapy.

What is clear is that if endoscopic therapy is undertaken, commitment is required by the endoscopist, clinical care team, and, most importantly, the patient. Endoscopic debridement is a time-consuming, labor-intensive process not for the uncommitted [40] or faint of heart since adverse events occur more commonly than in any other pancreaticobiliary intervention and have the potential to be fatal. Therefore, even more importantly, perhaps, is the need for support from intensivists, endoscopists, surgeons, and interventional radiologists to manage these complicated patients.

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