Infected Necrotizing Pancreatitis: Evolving Interventional Strategies From Minimally Invasive Surgery to Endoscopic Therapy—Evidence Mounts, But One Size Does Not Fit All

See "An endoscopic transluminal approach, compared with minimally invasive surgery, reduces complications and costs for patients with necrotizing pancreatitis," by Bang JY, Arnoletti JP, Holt BA, et al, on page 1027; and "Superiority of step-up approach vs open necrosectomy in long-term follow-up of patients with necrotizing pancreatitis, by Hollemans RA, Bakker OJ, Boermeester MA, et al, on page 1016.

Necrotizing pancreatitis occurs in ≤10%–20% of all patients with acute pancreatitis and portends a severe course of the disease.[1] Pancreatic and peripancreatic necroses may strike a dual blow: (1) by causing sterile systemic inflammatory response syndrome and (2) by providing a fertile ground for microorganisms, resulting in infected necrosis and sepsis.[1] Sterile systemic inflammatory response syndrome is due to the release of damage-associated molecular patterns from necrotic cells that lead to immune activation and release of cytokines.[2] Systemic inflammation, when severe, may lead to organ failure, which is the cause of most mortality in patients with acute pancreatitis. Infection of necrotic fluid collections is an ominous development during the course of necrotizing pancreatitis, and is an independent determinant of survival. Infection may develop any time during the disease process, but mostly occurs beyond the second week of illness.[1] The revised Atlanta classification defines necrotic collections of <4 weeks duration as acute necrotic collections.[3] As part of the body's reparative processes, the necrotic areas gradually become localized and walled off, known as "walled off necrosis." The distinction between acute necrotic collections and walled off necrosis has major implications for the treatment of patients with infected necrosis. There is a correlation between the extent and infection of necrosis, and organ failure, which may either precede (mostly) or follow infected necrosis.[4] The outcome of patients with infected necrosis is worse in those with than in those without organ failure.[5]

In the past, interventions for acute necrotizing pancreatitis were the domain of open surgery,[6] which was eventually abandoned for sterile necrosis after Bradley and Allen[7] showed in a seminal paper that outcomes of patients treated nonoperatively were better. Infected necrosis was still thought to mandate open surgery, until it was reported that many patients with infected necrosis could be treated without surgery by catheter drainage and antibiotics with similar results.[8] Then, the landmark Dutch multicenter, randomized PANTER trial showed that step-up therapy from percutaneous catheter drainage to minimally invasive surgery as required, done through video-assisted retroperitoneal debridement (VARD), was as effective as open surgery, but with less organ failure, hernia, diabetes, and other complications.[9] An important observation in that study was that one-third of patients recovered with antibiotics and percutaneous catheter drainage without a need for necrosectomy. It also established that minimally invasive necrosectomy is the preferred option in patients with appropriate anatomy who required intervention. This observation has subsequently been validated.[10]

Simultaneous developments in endoscopic transluminal therapy of pseudocysts and necrotic collections paved the way for a natural orifice approach to necrosectomy, including for infected necrosis.[11,12] Endoscopic cystogastrostomy has previously been shown to have equal efficacy, but with shorter hospital stay, better physical and mental health of patients, and lower cost than open surgical cystgastrostomy for drainage of pseudocysts.[13] Among the various minimally invasive surgical techniques, laparoscopy has also been used for necrosectomy, but with limited applications.[11,14] Multiple case series have suggested the efficacy of endoscopic transluminal drainage and necrosectomy for necrotic collections.[11,12] However, endoscopic necrosectomy had not been compared with minimally invasive surgery until recently.

Two studies on the evolving treatment of infected necrosis published in the current issue of *Gastroenterology* add substantially to our knowledge regarding this challenging problem. The MISER trial by Bang et al[15] prospectively compared endoscopic transluminal drainage and necrosectomy with minimally invasive surgery; the study by Hollemans et al[16] analyzed long term outcomes of patients previously randomized to minimally invasive step-up therapy (VARD) compared with open surgery in the PANTER trial.

In the trial by Bang et al, the composite primary outcome (new-onset organ failure, enteral or pancreatic-cutaneous fistula, bleeding, perforation of visceral organ, or death during a 6-month follow-up) was significantly less frequent in the endoscopy group compared with the minimally invasive surgery group (11.8% vs 40.6%; risk ratio, 0.29; $P = .007$) in patients with suspected/proven infected necrosis. As in most individual randomized trials comparing treatment strategies, there was no significant difference in all-cause mortality (8.8% vs 6.3%; $P = .9$). However, costs

Table 1. Summary of 2 Recent Randomized, Controlled Trials Comparing Endoscopic and Minimally Invasive Surgical Step-Up Approach for Suspected/Proven Infected Necrosis

	TENSION Trial		MISER Trial	
	Endoscopic	Surgical	Endoscopic	Surgical
No. of patients	51	47	34	32
Percent infected necrosis	23 (45%)	27 (57%)	31 (91%)	30 (94%)
Outcomes				
Composite end point	22 (43%)	21 (45%)	4(12%)	13(41%)
New-onset organ failure				
Single	7 (14%)	13 (28%)	NR	NR
Multiple	2 (4%)	6 (13%)	2 (6%)	3 (9%)
Death	9 (18%)	6 (13%)	3 (9%)	2 (6%)
Complications				
Bleeding	11 (22%)	10 (21%)	0	3 (9%)
Perforation	4 (8%)	8 (17%)	0	0
Fistula (pancreatic)	2/42 (5%)	13/42 (32%)	0	9 (28%)

NR, not recorded.

were lower and quality-of-life scores were better in the endoscopy group. VARD, by definition, will create at least a temporary externally drained pancreatic fistula and if one does not include fistula rate (0% and 28%) in the composite outcome, the 2 treatments were similar. The minimally invasive surgery group included both laparoscopic cystogastrostomy with necrosectomy in majority, and VARD in some patients. The choice was at the discretion of the surgeon and tailored to the individual patient, which might be considered a more pragmatic approach, although at the cost of heterogeneity in the surgical group. The approach in the endoscopic group was also heterogenous, with multiple transluminal gateways in the majority of patients, and the use of multiple plastic stents in some patients and metal stents in others. Such a tailored approach both in the endoscopy and surgical groups may make the results generalizable to a wider group of patients than a strictly regimented approach. Fistulae may result in substantial morbidity, and often require prolonged hospitalization and intervention, and thus merit inclusion as a major end point. Fistulae, observed exclusively in the surgical group, were likely a consequence of external drainage and intervention, whether percutaneous or minimally invasive surgical.

The results of the MISER trial can be compared with another recently published randomized trial comparing endoscopic transluminal therapy with minimally invasive surgery, the TENSION trial.[17] Important differences between these studies, which may influence decisions about best practice, are summarized in Table 1. The most important difference is that the MISER study included fistulae in the major composite end point, whereas the Dutch study did not, in large part explaining the disparity in conclusions. The MISER Trial showed that the endoscopic approach was superior and the Dutch study concluded that the endoscopic approach and minimally invasive step-up were similar. In addition, the Dutch study included relatively stable patients at a median of 6 weeks after the onset of illness with 70% having walled off necrosis and 30% partially walled off necrosis. The mean SOFA score, a measure of organ failure, was 0 or 1, suggesting stable patients. In the MISER trial also, patients had walled off necrosis, even though the mean time to intervention was 4 weeks, so that a significant number of patients underwent intervention before that interval. Inclusion of a high proportion of patients in American Society of Anaesthesiologists classes 3 and 4, and 29% patients with organ failure is a strength of the MISER trial, which lends support to the concept that the endoscopic approach could be effective even in sick patients. The mortality in the MISER trial was quite low at 8% despite the inclusion of very ill patients. This admirably low mortality may be due to early aggressive treatment, or a different patient profile. Although the primary determinant of mortality in infected necrosis is persistent organ failure,[4,5] a pooled and risk-adjusted analysis has suggested that endoscopic and minimally invasive surgical approaches may be independently associated with lower mortality than open surgery.[18] The advent of minimally invasive techniques coupled with intensive care should enable us to strive for single digit mortality in patients with infected necrosis.

Another issue that needs to be considered is the timing of intervention in patients with suspected infected necrosis. Open surgical necrosectomy has been shown in a randomized, controlled trial to have a worse outcome if performed before 4 weeks.[19] The same cut-off is generally recommended for percutaneous catheter and endoscopic transluminal drainage. However, a recent study has shown that early endoscopically centered intervention (<4 weeks) in the face of clinical deterioration with organ failure provided acceptable results without any difference in complications, compared with standard intervention after 4 weeks.[20] Of the 193 patients who required intervention in that study, 76 underwent early and 117 standard intervention. As compared with standard intervention, early intervention was more often performed for infected necrosis with deteriorating organ failure, which improved dramatically after intervention in both groups. Early endoscopic intervention was performed in a

substantial number of patients without encapsulation of the collection. There was significantly higher mortality (13% vs 4%; $P = .02$) and need for rescue open necrosectomy (7% vs 1%; $P = .03$) in the early intervention group, which were attributed to sicker patients, and more refractory and extensive collections, but were not the result of complications of endoscopic or percutaneous catheter intervention. It has been suggested that acute necrotic collections may wall off within 3 weeks in up to 43% of patients.[21] Thus, it remains unclear at what stage patients with infected necrosis and clinical deterioration should undergo percutaneous catheter drainage, endoscopic transluminal drainage, or both, and not be stalled further with medical management.

An additional issue in relation to infected necrosis is the need for necrosectomy in patients who show improvement after drainage. Overall one third to half of patients in the 2 randomized, controlled trials recovered with either percutaneous or endoscopic drainage alone,[9,17] although this fraction is substantially lower in other series, in which $\leq$80% of patients fail aggressive dual modality drainage alone and require endoscopic or other means of necrosectomy.[11,12,19] Large areas of necrosis, poor liquefaction, diffuse and multifocal collections, and the presence of organ failure are some of the important factors that govern response to drainage alone.[9,11,17] It must be appreciated that infected necrosis is a catabolic state, and source control is essential in those whose nutritional status is poor. Otherwise, some patients will deteriorate beyond the point of salvage, especially those with multiorgan failure.

Necrotizing pancreatitis is a devastating disease that results in long term morbidity and problems—subjects that have rarely been investigated in prospective studies. The original landmark randomized trial by van Santvoort et al[9] (the PANTER trial), reported on in 2010, found that a minimally invasive step-up approach was associated with a significantly lower composite end point of major morbidity and mortality than an open surgical approach. Hollemans et al[16] have reported the long-term follow-up of patients in that study who survived the illness after the index intervention. Of the 88 patients, 73 were alive and followed for a mean of 86 months. The primary outcome was similar to the original PANTER trial, consisting of a composite of major complications or death. Nineteen patients (44%) died or had major complications in the step-up group compared with 33 patients (73%) in the open necrosectomy group ($P = .005$). Significantly lower proportions of patients in the step-up group had incisional hernias (23% vs 53%; $P = .004$), pancreatic exocrine insufficiency (29% vs 56%; $P = .03$), or endocrine insufficiency (40% vs 64%; $P = .05$). A major reason for improved outcomes might be that necrosectomy was not required in 35% of the minimally invasive group, compared with all patients in the open group. There were no significant differences between the groups in proportions of patients requiring additional drainage procedures (11% vs 13%; $P = .99$), recurrent pancreatitis, or need for pancreatic surgery to treat long-term complications such as disconnected duct (11% vs 5%; $P = .43$). These data are reassuring and should be taken into consideration when advising patients about the choice of therapy. Even though the study showed reasonably good outcomes, long-term sequelae of necrotizing pancreatitis are well known. In a study of 578 patients, complications such as disconnected pancreatic duct syndrome (47.4%), splanchnic vein thrombosis (44.9%), insulin-dependent endocrine insufficiency (35.3%), exocrine insufficiency (18.9%), biliary stricture (15.6%), chronic pancreatitis (9.8%), chronic pain syndrome (7.7%), and gastrointestinal fistula (7.3%) were observed (N.J. Zyromski, unpublished data). These data suggest a need for periodic surveillance and continued care over an extended period of time. Many interventionalists, and especially endoscopists newly engaged in the field of necrotizing pancreatitis, might lose contact with patients after the initial intervention seems to be complete.

With these advances, we must appreciate gaps in our current knowledge, such as the variable clinical trajectory of acute necrotizing pancreatitis, the need to develop objective metrics for time to step-up therapy, and the need for better outcome measures particularly in mid and long-term. These outcome measures should include return to functional activity and quality of life.

Is open surgery "over and out"? Open surgery may still be required for patients with extensive necrosis who fail minimally invasive surgery, those with complications of pancreatitis such as bowel perforation, and complications of index intervention, such as endoscopy/laparoscopy-induced perforation and hemorrhage.[22] In 1 center with a 10-year history of aggressive endoscopically centered minimally invasive multimodal intervention for necrotizing pancreatitis, applied to nearly 300 patients, fully 7% of patients undergoing early intervention at $<$4 weeks required open surgery for salvage of refractory necrosis, or complications such as bowel perforation.[20]

What approach should we recommend for patients with infected necrosis? In those who are stable, but intervention is required because of clinical deterioration, either endoscopic drainage or a step-up approach with percutaneous drainage followed by VARD should be undertaken, depending on local expertise and the location of the collection. In patients with collections unsuitable for endoscopic drainage, percutaneous drainage should be the preferred approach. Percutaneous drainage is likely to provide at least short-term benefit to stabilize the majority of patients and may avoid further intervention in up to one-third of patients.[9] In selected patients with infected necrosis, a meta-analysis has shown that 64% could be treated successfully without the need for necrosectomy.[23] It should be noted that in both the MISER and TENSION trials, the endoscopically treated group was often treated before randomization, or after endoscopic intervention, with adjunctive percutaneous catheter drainage. Percutaneous drainage also provides opportunity for percutaneous endoscopic necrosectomy through the sinus tract.[12,24] The importance of dual modality drainage, which is so often required for ill patients with extensive extrapancreatic

necrosis, should not be overlooked by endoscopists jumping to conclusion that endoscopic therapy stands alone.

Infected necrosis is a heterogeneous disease with marked variation in extent and course, such that "one size" treatment does not fit all. Both the TENSION and MISER trials included very selected groups of patients, and importantly, both trials were conducted by experienced groups with multidisciplinary input and support. Acute necrotizing pancreatitis is a disease that mandates a holistic team approach with a team comprised of GI physicians, endoscopists, interventional radiologists, intensivists, and surgeons to develop an individualized approach to each patient.[22] Also, critical to the management of these patients is appreciation for the "long-term acute" disease process. Most patients will require care for months (and some up to and beyond 1 year) until resolution of the acute disease process. A dedicated team of physicians is necessary to follow this disease to completion, as well as to provide longer term interval follow-up of patients.

In summary, the study by Bang et al[15] provides robust evidence that endoscopic therapy may be preferred over minimally invasive surgical approaches when performed by expert hands at specialized centers. The follow-up study by Hollemans et al[16] has shown convincingly that minimally invasive approaches result in better long-term outcomes compared with open surgery in patients with infected necrosis. How the many modalities are integrated best for any individual patient, and at which centers and with which type of specialized team, still requires very careful consideration.

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Cooling Down the Hot Potato: Anti-Interleukin 36 Therapy Prevents and Treats Experimental Intestinal Fibrosis

See "Inhibiting interleukin 36 receptor signaling reduces fibrosis in mice with chronic intestinal inflammation," by Scheibe K, Kersten C, Schmied A, et al, on page 1082.

The majority of patients with Crohn's disease (CD) experience fibrosis associated complications over their lifetime culminating in need for resection.[1] Increasing evidence suggests that fibrosis is also common and clinically relevant in the colon of patients with ulcerative colitis, with clinical implications such as urgency or diarrhea.[2] Intestinal fibrosis represents perhaps the most significant remaining challenge in the field of inflammatory bowel diseases (IBD) because specific antifibrotic therapies are currently not available.[1] Intestinal mesenchymal cells (including fibroblasts, myofibroblasts, and smooth muscle cells) are considered the main effector cells in intestinal fibrosis through their ability to secrete extracellular matrix.[1] They can be activated by soluble factors, such as cytokines, chemokines, and growth factors from neighboring cells, including immune and nonimmune cells (epithelial cells, endothelial cells, fat cells). If excessive, this process ultimately leads to accumulation of extracellular matrix molecules such as collagens or fibronectins and increased tissue stiffness.[3]

Recently, IL-36 cytokines (IL-36α, IL-36β, and IL-36γ) were identified as potent activators of fibroblasts in the pancreas and kidney, making IL-36 and its downstream signaling pathways a potential target for the treatment of inflammation and fibrosis.[4,5] As a member of the IL-1 family, IL-36 transduces signals via binding to a heterodimeric receptor complex composed of IL36R and its co-receptor IL-1R accessory protein (IL-1RAcP).[6] Previous studies in IBD indicate that IL-36R signaling is activated in the IBD mucosa.[7] Inhibition of IL-36R signaling exhibited reduced disease severity in acute dextran sodium sulfate (DSS) and *Citrobacter rodentium* colitis in one study,[8] but caused worsening of acute DSS colitis and an impairment of wound healing in other studies.[7,9,10] This raised concerns about the therapeutic use of this pathway in human IBD, which made anti-IL36 therapy a potentially "hot potato."

In this issue of *Gastroenterology*, Scheibe et al[11] performed a timely investigation of a putative role of IL-36R signaling in chronic intestinal inflammation and fibrosis (Figure 1).[11] IL-36α–positive, but not IL-36γ–positive cells, were found to be increased in stenotic CD regions compared with controls, and were located adjacent to α-smooth muscle actin–positive myofibroblasts and smooth muscle cells. Cells expressing IL-36α were positive for CD14, CD64, and CD163, indicating that they are inflammatory and tissue-resident macrophages. RNA sequencing in both human and murine samples revealed IL-36R signaling as a regulator of fibrosis and tissue remodeling genes. Chronic systemic administration of IL-36R ligands increased the number of α-smooth muscle actin–positive cells. In 2 commonly accepted chronic experimental colitis and fibrosis models, trinitrobenzene sulfonic acid and DSS, both defective IL-36R signaling (mice deficient in IL36R) and preventive blockade of IL-36R signaling (via antibody injection) decreased intestinal inflammation and fibrosis. Importantly, antibody-mediated inhibition of IL-36R reversed the established experimental intestinal fibrosis and also ameliorated inflammation.[11] IL-36R is expressed on cell types other than fibroblasts, including immune cells, which could indirectly contribute to fibrosis.[11] The authors of the current study elegantly used bone marrow chimeras to show that IL-36R signaling in the hematopoietic compartment is not critical in experimental fibrogenesis.