Outcomes of early endoscopic intervention for pancreatic necrotic collections: a matched case-control study CME

Nicholas Oblizajek, MD,[1] Naoki Takahashi, MD,[2] Sevda Agayeva, MD,[1] Fateh Bazerbachi, MD,[1] Vinay Chandrasekhara, MD,[1] Michael Levy, MD,[1] Andrew Storm, MD,[1] Todd Baron, MD,[3] Suresh Chari, MD,[1] Ferga C. Gleeson, MB, BCh,[1] Randall Pearson, MD,[1] Bret T. Petersen, MD,[1] Santhi Swaroop Vege, MD,[1] Ryan Lennon, MS,[4] Mark Topazian, MD,[1] Barham K. Abu Dayyeh, MD, MPH[1]

Rochester, Minnesota

Background and Aims: Pancreatic necrosis may be categorized as an acute necrotic collection (ANC) or walled-off necrosis (WON) based on complete encapsulation by a wall and collection age (≤4 weeks or >4 weeks). Endoscopic intervention of WON has become the standard of care, but little is known regarding the safety and efficacy of endoscopic intervention of pancreatic necrosis ≤4 weeks from disease onset.

Methods: Retrospective review of medical records and imaging studies of all patients undergoing early endoscopic intervention of pancreatic necrosis between 2008 and 2018 was carried out at 1 referral center. Patients who underwent previous interventional treatment were excluded. Control WON patients were matched to early intervention cases. The primary outcome was defined as resolution of the collection after endoscopic treatment, without surgery.

Results: Nineteen patients with early intervention were identified. The most common indication for intervention was infection. Median age of these collections at the time of initial endoscopic intervention was 23 days (range, 15-27 days), and all collections had a partial or complete wall discernable on contrast-enhanced CT. Eleven patients underwent concurrent endoscopic necrosectomy. The primary outcome was achieved in all patients in the early intervention group. Total duration of therapy was longer for early intervention compared with controls (103 vs 69 days, $P = .042$), with no mortality and similar adverse event rates compared with controls.

Conclusions: Endoscopic intervention of pancreatic necrosis in the third and fourth weeks of illness appears effective and safe when a partial collection wall is present on cross-sectional imaging studies, with outcomes paralleling those reported for intervention of WON. (Gastrointest Endosc 2020;91:1303-9.)

Abbreviations: ANC, acute necrotic collection; CECT, contrast-enhanced computed tomography; ICU, intensive care unit; WON, walled-off necrosis.

DISCLOSURE: *Dr Chandrasekhara has served on a medical advisory board for Interpace Diagnostics and is a shareholder in Nevakar Corp. Dr Storm has been a consultant for GI Dynamics and has received research support from Endo-TAGSS, Boston Scientific, Apollo Endosurgery. Dr Baron has served as a consultant and speaker for BSCI, Cook Endoscopy, Olympus, W.L. Gore, and Medtronic. Dr Petersen has served as an investigator and consultant for Boston Scientific and as a consultant for Olympus America, Pentax, Inc, GIE Medical, and AMBU. Dr Vege has written for UpToDate and was involved as an investigator in the NIH CPPDC consortium trial. Dr Abu Dayyeh has served as a consultant for Boston Scientific, Metamodix, BFKW, DyaMx, and USGI Medical, has received research support for Boston Scientific, Apollo Endosurgery, USGI, Spatz Medical, GI Dynamics, Caim Diagnostics, Aspire Bariatrics, and Medtronic, and has been a speaker for Johnson & Johnson, Endogastric Solutions, and Olympus. The other authors disclosed no financial relationships.*

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Current affiliations: Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota (1); Division of Radiology, Mayo Clinic, Rochester, Minnesota (2); Division of Gastroenterology and Hepatology at University of North Carolina, Chapel Hill, North Carolina (3); Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA (4).

Reprint requests: Barham K. Abu Dayyeh, MD, MPH, Associate Professor of Medicine, Director of Advanced Endoscopy, Consultant in Gastroenterology and Hepatology, Mayo Clinic – Rochester, 200 First Street SW, Rochester, MN 55905.

INTRODUCTION

Up to 20% of patients with acute pancreatitis will develop necrosis,[1] which may be categorized as either an acute necrotic collection (ANC) or walled-off necrosis (WON). An ANC has "no definable wall encapsulating the collection," whereas WON is a mature collection that is "completely encapsulated" by a "well-defined wall."[2] International consensus criteria state that maturation of a WON usually or always requires 4 weeks after onset of acute necrotizing pancreatitis.[2,3] Many patients with pancreatic necrosis require intervention for adverse events such as infection, GI obstruction, or persistent pain and inability to eat.[4] Current international guidelines advise postponing invasive interventions for pancreatic necrosis until the stage of WON has been reached, at least 4 weeks after disease onset.[3,5,6] However, in up to 30% of patients, infection of pancreatic necrosis is clinically recognized before the fourth week of illness.[7-11] Some experts advise antibiotic treatment alone or percutaneous drainage in such cases.[12] Despite conservative measures, some of these patients will require early intervention of their collection.

There are few published data assessing the efficacy and safety of endoscopic treatment of pancreatic necrosis that is less than 4 weeks old. Trikudanathan and colleagues[13] recently reported higher mortality and need for rescue surgery after endoscopic intervention of necrotic pancreatic collections <4 weeks old compared with collections >4 weeks old. This study included patients who had undergone previous percutaneous drainage and did not report the time from onset of symptoms to intervention or detailed imaging characteristics of the walls of necrotic collections. The aim of the present study was to retrospectively evaluate the safety and efficacy of endoscopic treatment of pancreatic necrosis less than 4 weeks after disease onset, with a particular focus on timing of early intervention and imaging features of treated collections.

METHODS

This is a retrospective review of all patients with acute pancreatitis who underwent attempted endoscopic intervention of pancreatic necrosis at Mayo Clinic in Rochester, Minnesota, within the first 28 days of illness. Potential patients who were cared for between 2008 and 2018 were identified from medical record and endoscopy databases. The date of initial onset of pancreatitis symptoms (which may have preceded the date of hospitalization) was considered day 1. Patients were included if (1) they had definite pancreatic and/or peripancreatic necrosis on contrast-enhanced computed tomography (CECT) performed before endoscopic intervention, (2) they had clinical signs, symptoms, and laboratory findings consistent with pancreatitis with known date of symptom onset, and (3) endoscopic intervention was attempted on or before 28 days after the onset of symptoms. Patients were excluded who (1) had a history or imaging findings of chronic pancreatitis, (2) had a history of previous pancreatic surgery or interventional treatment of pancreatitis, (3) had percutaneous or surgical drainage of the necrotic collection performed before attempted endoscopic intervention, (4) had evidence of a spontaneous fistula between the necrotic collection and GI tract that formed before attempted endoscopic intervention, or (5) had unknown age of collection or unknown definitive date of symptom onset by chart review. The study was approved by the Mayo Clinic Institutional Review Board.

Several databases were reviewed to identify patients, including endoscopic databases and electronic medical record queries. Data were abstracted regarding clinical, laboratory, and imaging findings, and endoscopic procedure notes were reviewed. Imaging data were abstracted from CECT images by a single expert abdominal radiologist (N.T.) who was blinded to case/control status of the included patients. Clinical outcomes and adverse events were identified by medical record review and by querying medical records with specific text commands.

The patient's date of symptom onset was determined by medical record review. Cases for which no clear date of symptom onset could be identified were excluded. Symptom resolution was determined by medical record review, and collection resolution was determined by dedicated radiologic review of follow-up imaging. If patients were lost to follow-up and thus had no follow-up imaging, they were excluded from the study. The primary outcome of interest was the resolution of the necrotic collection on cross-sectional imaging after intervention, defined as a decrease in collection diameter to that of the indwelling portion of the transmural stents, without need for surgery. Imaging data were abstracted from CECT images by a single investigator (N.T.) blinded to case/control status for the 19 cases of early intervention (≤4 weeks) and 19 control cases of late (>4 weeks) endoscopic intervention. Controls were chosen from an institutional research database of individuals who required endoscopic intervention of WON >4 weeks after onset of illness and were matched to cases by gender, age (±5 years), suspected infected necrosis before intervention (yes/no), and collection maximum diameter (±30%). In most cases, there was a single best match based on the aforementioned criteria, but in the few cases where more than 1 control was available for matching to a case, the control with intervention occurring on the calendar date closest in time to the case was used.

The presence and characteristics of the collection wall were determined by expert review of contrast-enhanced CT scans performed before initial endoscopic intervention. A collection wall was considered present in regions

where there was a discrete smooth margin between the collection and adjacent tissue and was rated both for its completeness (complete, partial, or absent) and thickness (thick or thin). Areas with an irregular or indistinct margin between the collection and adjacent soft tissue were considered not to have a wall. The wall was considered complete if >80% of the collection was encapsulated by a wall and was considered partial if between 20% and 80% of the collection was encapsulated. The wall was considered thick when it was well defined and demonstrated contrast enhancement and was considered thin when it had no appreciable contrast enhancement.

Conditional logistic regression was performed using JMP Pro version 14.1.0 (SAS Institute, Cary, NC, USA) to compare cases and controls with regard to clinical data, imaging features of their collections, procedure characteristics, and outcomes. Confidence intervals for binomial outcomes were calculated at a 95% confidence level using the method by Wilson.[14]

RESULTS

Among 161 patients undergoing endoscopic intervention of pancreatic necrosis during the study period, we identified 24 who underwent attempted intervention within 28 days of symptom onset. Among these, 5 were excluded because no CECT was performed before intervention (1 patient), there was spontaneous drainage (fistulization) to the gut before intervention (1 patient), there was loss to follow-up (2 patients), and date of symptom onset was unclear after further chart review (1 patient). A total of 19 early intervention patients were therefore included in the data analysis and matched with WON controls.

Demographics and clinical characteristics are shown in Table 1. All 19 early intervention cases had both pancreatic and peripancreatic tissue necrosis seen on CECT. The commonest indication for intervention was infection, and no patient underwent early intervention for pain alone. A total of 11 early intervention cases required intensive care unit (ICU) level care during their hospitalization; 5 of these patients were in the ICU at the time of their index procedure. Comparatively, 2 late intervention controls required ICU level care; 2 were in the ICU at the time of their index procedure.

Figure 1 illustrates typical imaging features of CECT performed before endoscopic intervention in the study cohort, and Table 1 summarizes the radiologic characteristics of the collections. Early intervention cases were less likely to have a complete wall than late intervention cases at the time of initial intervention (8 of 19 vs 17 of 19, $P < .01$ by conditional logistic regression).

Procedure characteristics of the initial endoscopic intervention are shown in Table 2. No patients had undergone previous percutaneous or surgical intervention for their pancreatic necrosis. Of the 19 patients, 11 underwent transduodenal drainage at the time of the initial endoscopic intervention, often in combination with transgastric drainage (5 patients). About 50% of cases and controls received plastic stents only. The metal stents that were used to perform cystenterostomy evolved over the course of the study, and included Niti-S (Taewoong Medical, Seoul, South Korea), Alixmaxx-ES (Merit Medical, South Jordan, Utah), and Axios (Boston Scientific, Marlborough, Mass, USA) stents.

Table 3 shows patient outcomes and adverse events. The primary study outcome of resolution of the necrotic collection on cross-sectional imaging after intervention and without surgery was achieved in all cases (95% confidence interval, 83%-100%). Eleven patients (58%) who underwent early intervention had endoscopic necrosectomy during their index procedure, and all cases required endoscopic necrosectomy at some point during their treatment course. In both the case and control cohorts, 3 patients (16%) each were treated for disconnected duct syndrome with pancreatic duct stent placement. Positive collection microbial culture results were noted in 68%. Adverse events likely related to the initial or subsequent endoscopic intervention occurred in 21% of the early intervention cases, compared with 32% of late intervention controls ($P = .41$). There was no mortality in the study group during the 1 year period after initial treatment, and there were no significant differences between early intervention cases and late intervention controls with regard to adverse event rates or need for percutaneous drainage. One early intervention patient ultimately required surgical intervention for management of disconnected pancreatic duct syndrome. This patient's necrotic collection resolved after endoscopic treatment, but the patient ultimately required distal pancreatectomy, splenectomy, and cholecystectomy 65 days after the initial endoscopic intervention for persistent symptoms related to disconnected pancreatic duct syndrome.

Among the early intervention cases identified, 2 patients unfortunately had to be excluded because they did not meet study criteria because they were lost to follow-up, and thus the resolution of their disease could not ultimately be determined. For these 2 cases, the age of the collection at the time of the initial endoscopic intervention was 26 and 28 days versus a median of 22 days in those with a successful outcome (range, 15-27 days), and a complete wall was not present on CECT in either of these 2 patients versus 8 of the 19 patients who had a successful outcome. The first patient lost to follow-up underwent transgastric endoscopic intervention of a 16 cm collection 26 days after symptom onset and subsequently required interventional radiology-guided drainage of a left iliopsoas muscle abscess that resulted from a disconnected pancreatic duct. Ultimately, this patient underwent 4 endoscopic treatment sessions (necrosectomy, additional drainage, or stent removal) and was lost to follow-up. At the last

TABLE 1. Clinical and imaging features of the 19 patients with early intervention undergoing endoscopic intervention, and matched walled-off necrosis controls

	Early intervention cases (n = 19)	Late intervention controls (n = 19)	*P* value
Age (years), median (range)	64 (21-79)	56 (28-86)	.58
Gender (female), n (%)	6 (32)	6 (32)	1.00
Body mass index (kg/m^2), median (range)	29.5 (20.7-43.0)	27.4 (19.7-46.2)	.58
History of previous pancreatitis, n (%)	5 (26)	2 (11)	.25
Indications for intervention, n (%)			
Infection	13 (68)	13 (68)	1.00
Pain	9 (47)	12 (63)	.17
Gastric outlet obstruction	0 (0)	1 (5)	.37
Nausea and vomiting	5 (26)	4 (21)	.57
Enlarging collection	6 (32)	4 (21)	.41
Bleeding in cyst	2 (11)	2 (11)	1.00
GI bleeding	1 (5)	0 (0)	.37
Cause of pancreatitis, n (%)			
Gallstone	8 (42)	10 (53)	.32
Alcohol	0 (0)	1 (5)	
Post-ERCP	2 (11)	0 (0)	
Unknown or other causes	9 (47)	8 (42)	
Size of the collection (cm), median (range)	16 (7-24)	15 (5-22)	.021
Collection age at time of intervention (days), median (range)	23 (15-27)	64 (32-2747)	
Wall characteristics			
Thick wall, n	17	18	.57
Thin wall, n	2	1	
Collection wall completeness on CT, n			<.01
Full	8	17	
Partial	11	2	
Collection wall at drainage site, n			.032
Thick	14	18	
Thin	5	0	
None		1	
Air in collection before intervention, n (%)	2 (11)	7 (37)	.049
Fat in collection before intervention, n (%)	17 (89)	12 (63)	.093
Number of initial endoscopic drainage sites, n (%)			
One drainage site	13 (68)	18 (95)	.014
Two drainage sites	6 (32)	1 (5)	
Location of drainage, n (%)			
Transgastric	8 (42)	15 (79)	.038
Transduodenal	6 (32)	3 (16)	
Both	5 (26)	1 (5)	

outpatient follow-up, the patient continued to have intermittent abdominal pain, and imaging showed an intrapancreatic fluid collection 4.8 × 3.5 cm. The second patient lost to follow-up underwent endoscopic intervention and necrosectomy of a 16 cm collection 28 days after symptom onset. At the patient's posthospital follow-up visit, his clinical symptoms had resolved except for mild loose stools 2 to 3 times daily, but due to the lack of follow-up imaging, no overall determination regarding procedure radiographic success could be made.

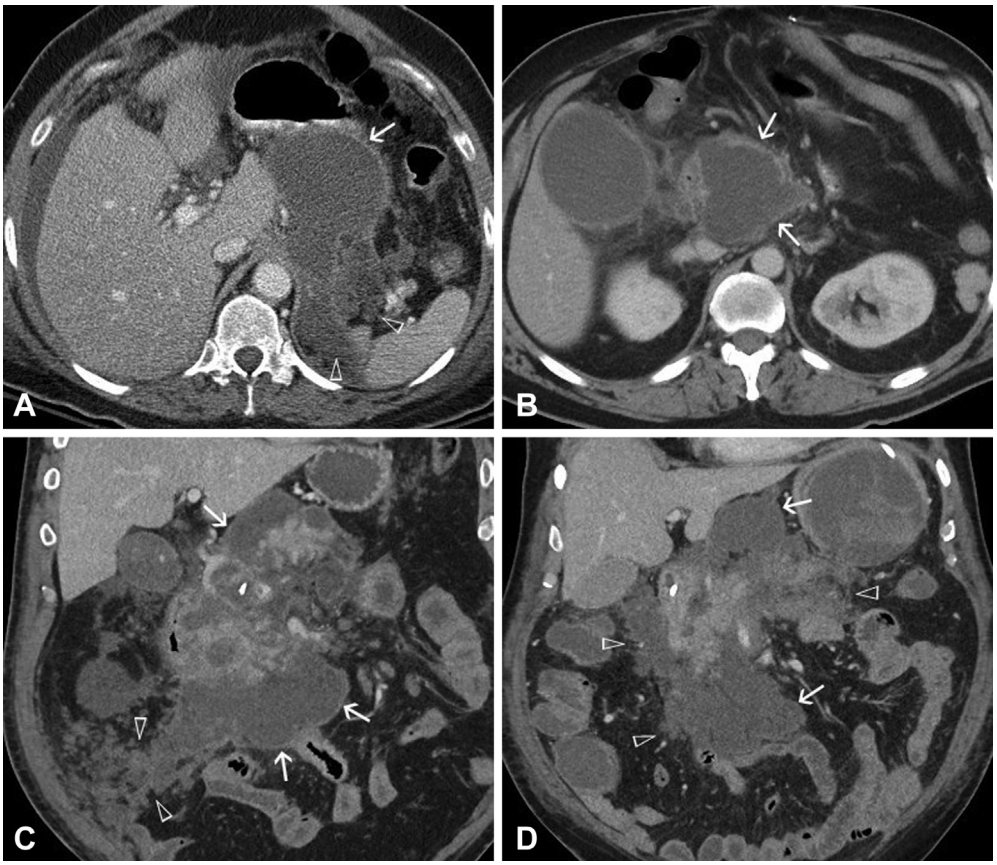

Figure 1. Contrast-enhanced CT scans of acute necrotic collections that underwent endoscopic intervention. *Arrows* indicate portions of the collection with a wall, and *arrowheads* indicate portions of the collection without a wall. **A**, Thick partial wall. **B**, Thick complete wall. **C**, Thick partial wall. **D**, Thin partial wall.

TABLE 2. Procedure characteristics of the 19 patients with early intervention undergoing endoscopic intervention and matched walled-off necrosis controls

	Early intervention cases (n = 19)	Late intervention controls (n = 19)	*P* value
Endoscopic necrosectomy during index intervention	11 (58)	15 (79)	.15
Total number of endoscopic necrosectomy sessions, median (range)	4 (1-9)	3 (1-11)	.71
Subsequent percutaneous drainage required	3 (16)	4 (21)	.66
Type of stents placed during index procedure			
Plastic	9 (47)	10 (53)	.18
LAM stent (Axios)	2 (11)	6 (32)	.18
Other metal stent (Niti-S, Alimaxx-ES)	2 (11)	0 (0)	.18
Plastic and LAM stent	6 (32)	2 (11)	.18
None	0 (0)	1 (5)*	.18
Mention of disrupted/disconnected duct on imaging or ERCP	9 (47)	8 (42)	.78
Pancreatic stent placement for disrupted/disconnected duct	3 (16)	3 (16)	1.00
Drainage stents left in place for disconnected/disrupted duct	0 (0)	1 (5)	.37
Distal pancreatectomy for disconnected/disrupted duct	1 (5)	2 (11)	.57

Values are number (%) except where indicated otherwise.
LAM, Lumen apposing metal.
*This patient was initially managed with a nasopancreatic tube with lavage.

TABLE 3. Outcomes of endoscopic intervention of the 19 patients with early intervention and matched walled-off necrosis controls

	Early intervention cases (n = 19)	Late intervention controls (n = 19)	*P* value
Resolution of symptoms	17 (89)	17 (89)	1.00
Resolution of the collection on cross-sectional imaging studies	19 (100)	18 (95)	.37
Primary outcome achieved	19 (100)	18 (95)	.37
Time from initial procedure to removal of all stents and drains (days), median (range)	103 (44-422), n = 18	69 (27-330), n = 17	.042*
Patients requiring surgery before stent removal	1 (5)	0 (0)	.37
Length of hospital stay† (days), median (range)	26 (6-44)	6 (0-40)	<.01
Number of ICU days† (days), median (range)	1 (0-22)	0 (0-6)	<.01
Number of ICU days before index intervention (days), median (range)	1 (0-18)	0 (0-4)	<.01
Number of ICU days after index intervention (days), median (range)	0 (0-21)	0 (0-2)	.092
Requiring ICU care at the time of index intervention	5 (26)	1 (5)	.093
Patients experiencing adverse events likely related to endoscopic intervention	4 (21)	6 (32)	.41
Stent migration	2 (11)	4 (21)	.15
Stent occlusion	2 (11)	2 (11)	1.00
Hemorrhage	1 (5)	3 (16)	.32
Aspiration pneumonitis	1 (5)	0 (0)	.37
Patients experiencing adverse events likely not related to endoscopic intervention	5 (26)	8 (42)	.36
New diabetes mellitus	2 (11)	1 (5)	.57
Venous thrombosis (portal/splenic/superior mesenteric vein)	4 (21)	5 (26)	.71
New varices (gastric or esophageal)	0 (0)	5 (26)	.014
Mortality (1 year)	0 (0)	1 (5)	.37

Values are number (%) except where indicated otherwise.
ICU, Intensive care unit.
*Only 16 cases/controls were used for the analysis due to lack of outcomes data.
†For the hospitalization during which initial endoscopic intervention was performed.

DISCUSSION

Endoscopic drainage with or without debridement has become an accepted modality for treatment of WON, but there are few published data regarding the safety and efficacy of early endoscopic intervention of pancreatic necrosis ≤4 weeks after disease onset. In this study, we found that early endoscopic intervention of necrotic collections 15 to 27 days after pancreatitis onset had similar efficacy and safety compared with endoscopic intervention of WON.

A recent, larger series by Trikudanathan et al[13] was the first to report outcomes of early endoscopic intervention of necrotic collections. A heterogeneous group of patients was studied, including patients undergoing initial percutaneous drainage, and time from onset of pancreatitis symptoms to initial intervention was not reported. Compared with patients undergoing intervention of WON, there was significantly increased length of hospital stay, length of ICU stay, percutaneous drainage (42% vs 21%), surgery (7% vs 1%), and mortality (19% vs 5%) in the group who underwent early endoscopic intervention. We similarly found that patients undergoing early endoscopic intervention of necrosis had more frequent and longer ICU stays and longer duration of interventional treatment compared with WON controls. However, we found no increase in mortality, rescue surgery, or percutaneous drainage and observed a trend toward fewer adverse events after early endoscopic intervention compared with late intervention controls. Our study demonstrates the feasibility and safety of endoscopic intervention of necrotic collections as early as 15 days after an inciting episode of pancreatitis with creation of multiple drainage sites and both transduodenal and transgastric drainage, with use of plastic and/or metal stents, without previous percutaneous drainage.

Consensus definitions of necrotic pancreatic collections describe 2 ends of a spectrum: ANCs have no definable wall and are <4 weeks old, whereas WONs are fully encapsulated by a mature wall and are always or almost always >4 weeks old.[2,3] The evolution from ANC to WON occurs slowly, and clinicians often manage collections that do not fully meet either of these definitions. Trikudanathan and colleagues[13] reported "some," "extensive," or "complete" wall formation in 49%, 37%, and 7%, respectively, of their patients undergoing early endoscopic intervention, but

specific radiologic criteria defining the presence, thickness, and completeness of the collection wall were not described, nor was a blinded comparison of cases and controls used. We used standardized and objective imaging definitions of the presence, thickness, and completeness of a collection wall, and the study radiologist was blinded to case/control status. We found that most of our patients undergoing early intervention had a partial collection wall visible on CT, defined as a discrete smooth margin between the collection and adjacent tissue encapsulating 20% to 80% of the collection. If further validated, this definition may be useful to clinicians assessing the risks and benefits of early endoscopic intervention of symptomatic pancreatic necrosis.

Our results should not be extrapolated to patients in the first days of illness whose collection has not marginated. In addition, we believe that careful endoscopic technique must be used to minimize the likelihood of perforation of a necrotic collection by guidewires or necrosectomy devices in patients with a partial collection wall. With these caveats, our data suggest that early endoscopic intervention is an acceptable management strategy in a carefully selected patient population, with outcomes paralleling those seen in late intervention.

Although we matched early intervention cases and late intervention controls on the basis of age, gender, collection size, and indication for intervention, air was more commonly seen in late intervention cases, suggesting pre-existing fistulization to the gut, and it is possible that other factors differed between the groups and could have obscured differences in outcomes. However, all early intervention patients in this study did require urgent intervention, most commonly for a presumed infectious process without adequate source control with antimicrobial therapy alone. Despite increased severity of illness (manifested by the need for ICU care), we found that there were fewer overall adverse events associated with early endoscopic intervention compared with late intervention, although this difference was not statistically significant.

Limitations of this study include its retrospective design and the small sample size, reflecting our careful selection of patients requiring early endoscopic intervention of their necrotic collections. In addition, these procedures were performed by endoscopists highly experienced with pancreatic necrosis management at a single institution, which may bias our study toward positive outcomes. Few patients were lost to follow-up in the early intervention group, thus potentially influencing our reported adverse event rates and outcomes in this cohort. Strengths of our study include detailed case annotation and careful review of CT scan images by a radiology coinvestigator blinded to case/control status, using predefined imaging criteria.

A gap exists in our current understanding as to the exact correlation in wall thickness between CECT imaging with EUS findings in intervention. Noninvasive contrast-enhanced imaging may potentially underestimate the presence or characteristics of the wall around the necrosis. This does not represent a shortcoming of the radiologist or endoscopic interventionalist reviewing such images, but rather a potential area for improvement in imaging techniques. More sensitive future radiologic methodologies such as magnetic resonance may help to further our understanding of the optimal timing for endoscopic intervention of pancreatic necrosis, rather than defining maturity for endoscopic intervention based on time alone.

In conclusion, early endoscopic intervention of pancreatic necrosis in the third and fourth week after onset of pancreatitis appears safe and efficacious when there is a clinical indication for urgent intervention and CECT demonstrates a partial or complete collection wall.

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