Original article

Outcomes after implementing a tailored endoscopic step-up approach to walled-off necrosis in acute pancreatitis

J. Y. Bang[1], B. A. Holt[1], R. H. Hawes[1], M. K. Hasan[1], J. P. Arnoletti[2], J. D. Christein[3], C. M. Wilcox[4] and S. Varadarajulu[1]

Centers for [1]Interventional Endoscopy and [2]Specialized Surgery, Florida Hospital, Orlando, Florida, and [3]Department of Surgery and [4]Division of Gastroenterology–Hepatology, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to: Dr S. Varadarajulu, Center for Interventional Endoscopy, Florida Hospital, 601 East Rollins Street, Orlando, Florida 32803, USA (e-mail: svaradarajulu@yahoo.com)

Background: **The aim of the study was to compare the outcomes of patients with pancreatic or peripancreatic walled-off necrosis by endoscopy using the conventional approach *versus* an algorithmic approach based on the collection size, location and stepwise response to intervention.**

Methods: **This was an observational before–after study of consecutive patients managed over two time intervals. In the initial period (2004–2009) symptomatic patients with walled-off necrosis underwent conventional single transmural drainage with placement of two stents and a nasocystic catheter, followed by direct endoscopic necrosectomy, if required. In the later period (2010–2013) an algorithmic approach was adopted based on size and extent of the walled-off necrosis and stepwise response to intervention. The main outcome was treatment success, defined as a reduction in walled-off necrosis size to 2 cm or less on CT after 8 weeks.**

Results: **Forty-seven patients were treated in the first interval and 53 in the second. There was no difference in patient demographics, clinical or walled-off necrosis characteristics and laboratory parameters between the groups, apart from a higher proportion of women and Caucasians in the later period. The treatment success rate was higher for the algorithmic approach compared with conventional treatment (91 *versus* 60 per cent respectively; $P < 0{\cdot}001$). On multivariable logistic regression, management based on the algorithm was the only predictor of treatment success (odds ratio 6·51, 95 per cent c.i. 2·19 to 19·37; $P = 0{\cdot}001$).**

Conclusion: **An algorithmic approach to pancreatic and peripancreatic walled-off necrosis, based on the collection size, location and stepwise response to intervention, resulted in an improved rate of treatment success compared with conventional endoscopic management.**

Presented to Digestive Diseases Week, Chicago, Illinois, USA, May 2014; published in abstract form as *Gastrointest Endosc* 2014; **79**: AB373

VIDEO AVAILABLE ONLINE

Paper accepted 5 September 2014

Published online 21 October 2014 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9664

Introduction

Acute pancreatitis has an annual incidence of 13–45 per 100 000 people, and is one of the most common gastrointestinal disorders requiring hospital admission worldwide[1]. Pancreatic necrosis occurs in approximately 20 per cent of patients who have severe acute pancreatitis[2]. The resultant liquefaction of the pancreatic parenchyma can mature into a contained collection termed walled-off necrosis, which can be located within the pancreatic parenchyma or the peripancreatic tissue, and typically forms around 4 weeks into the disease course[3]. With intensive conservative management, including nutritional and intensive care support when required, the collection may resolve without intervention. However, a persistent collection causing pain, gastric outlet, intestinal or biliary obstruction, new-onset or persisting organ failure, or infection is associated with a mortality rate of 15–20 per cent, and requires necrosectomy and drainage[4].

Evidence suggests that minimally invasive surgical techniques are superior to laparotomy, with decreased rates of postoperative adverse events and long-term morbidity[5–8]. As an alternative to surgery, minimally invasive endoscopic techniques have also gained acceptance, with an adverse

event rate between 10·4 and 24·5 per cent[9–13]. Endoscopic approaches vary and have evolved over the past decade to include use of single or multiple transmural tracts with stents and nasocystic catheters for drainage and flushing, single or multiple percutaneous drainage catheters, and direct endoscopic or percutaneous necrosectomy[9–13].

Understanding of pancreatic fluid collections has evolved considerably[14]. Historically, a subgroup of patients with pancreatic fluid collections had poor clinical outcomes and the reason was not clear. With the development of high-resolution cross-sectional imaging and endoscopic ultrasonography (EUS), the type of pancreatic fluid collection could be defined more accurately in terms of the presence and amount of pancreatic necrosis and the maturity of the collection, and this distinction led to a more lesion-specific approach. Since 2009, several studies[15–17] have reported good outcomes for walled-off necrosis by combining endoscopic and percutaneous drainage, lavage and transluminal endoscopic necrosectomy. At the same time, the authors' group investigated the combined techniques of multiple transluminal gated pathways, percutaneous catheter drainage and percutaneous necrosectomy in a small number of patients. This approach was associated with good clinical response, which led to the development of an algorithmic approach incorporating these techniques for all subsequent patients with walled-off necrosis.

There are few data comparing the clinical outcomes of patients undergoing treatment of walled-off necrosis using the different endoscopic approaches that have evolved over time. Unlike uncomplicated pseudocysts that can be treated successfully with conventional transmural drainage in over 90 per cent of patients, walled-off necrosis is more complex with lower rates of treatment success and greater procedural morbidity[18–20]. A recent meta-analysis[21] of the management of walled-off necrosis showed comparable clinical outcomes with conservative and interventional approaches. Therefore, to maximize clinical success, endoscopic treatment of walled-off necrosis, if undertaken, must be structured to yield maximum clinical benefit. The objective of this study was to compare the clinical outcomes of patients with walled-off necrosis treated by two different endoscopic approaches.

Methods

All consecutive patients with walled-off necrosis who underwent endoscopic treatment over a 10-year interval from January 2004 to December 2013 at two tertiary medical centres in the USA were analysed retrospectively from a prospectively maintained database. Walled-off necrosis was defined as a mature encapsulated collection of pancreatic and/or peripancreatic necrosis that had developed a well defined inflammatory wall[3]. Patients were referred primarily by gastroenterologists and pancreatic surgeons from outside facilities in southern USA and in-house intensive care specialists.

Included in the study were patients aged more than 19 years with symptomatic walled-off necrosis measuring over 6 cm in size and located adjacent to the stomach or duodenum with evidence of ongoing infection (fever, leucocytosis, positive blood cultures), continued clinical deterioration or persistence of symptoms despite ongoing supportive measures, or gastric outlet obstruction owing to a mass effect of the walled-off necrosis.

Excluded from the study were patients with walled-off necrosis located more than 15 mm from the gastrointestinal lumen, coagulopathy or follow-up of less than 60 days. All patients provided written informed consent for undergoing endoscopic interventions and the study was approved by the hospitals' institutional review boards.

Treatment protocol

Patients were divided into two time intervals according to the type of treatment they received for walled-off necrosis (group 1, 2004–2009; group 2, 2010–2014). All patients underwent preprocedure contrast-enhanced CT of the abdomen and pelvis to define the extent of necrosis and to confirm that the necrotic collection had 'walled-off'. If a disconnected main pancreatic duct had not been demonstrated on magnetic resonance cholangiopancreatography, the patient underwent endoscopic retrograde cholangiopancreatography (ERCP) to assess duct integrity and place a bridging stent where technically possible. Intravenous antibiotics were administered before the procedure in all patients and continued for 48 h or until discharge. A percutaneous gastrojejunostomy feeding tube was placed in any patient unable to tolerate oral intake, and CT of the abdomen and pelvis carried out after 72 h to assess the treatment response.

Conventional approach (2004–2009)

Walled-off necrosis causing visible luminal compression was accessed using a therapeutic duodenoscope and needle-knife catheter. In patients without significant luminal compression, a therapeutic echoendoscope was used to identify the necrotic collection and access gained with a 19-G EUS needle. The transmural tract was dilated to 12–15 mm using a radial expansion balloon (CRE™; Boston Scientific, Natick, Massachusetts, USA) over a 0·035-inch guidewire, and two to three 7- or 10-Fr

double-pigtail stents (Cook Endoscopy, Winston-Salem, North Carolina, USA) were deployed sequentially. A 7-Fr nasocystic catheter was placed for cavity irrigation with 200–250 ml normal saline plus 80–120 mg gentamicin every 4–6 h. Direct endoscopic necrosectomy was performed using a double-channel gastroscope in patients with persistent symptoms and no significant decrease in collection size (less than 50 per cent decrease on abdominopelvic CT). Endoscopic necrosectomy was continued until most of the necrosis had been debrided and granulation tissue was evident. In selected patients with no clinical and/or radiological response to the above interventions, drainage was undertaken using the multiple transluminal gateway technique. With this technique, under EUS guidance, two to four transmural tracts were created between the walled-off necrosis and gastric or duodenal lumen, and were maintained by placement of multiple 7-Fr double-pigtail plastic stents. An 18-Fr nasocystic tube was also placed, although a 7-Fr nasocystic tube was used if technical difficulty was encountered. If the patient was persistently symptomatic or deteriorated clinically, surgical consultation was obtained for open necrosectomy.

Algorithmic approach (2010–2013)

Transmural drainage was undertaken using a therapeutic echoendoscope. The endoscopic approach was tailored to the collection size and location, and a stepwise approach was adopted in response to the intervention (*Fig. 1*). For unilocular walled-off necrosis no larger than 12 cm, a conventional endoscopic treatment approach was used, as for group 1 (*Fig. 2*). To treat walled-off necrosis larger than 12 cm, multiple internal conduits were created using the multiple transluminal gateway technique. An 18-Fr nasocystic tube was placed for irrigation and drainage (*Fig. 3*; *Video S1*, supporting information). For walled-off necrosis larger than 12 cm with extension to the flank(s), in addition to the multiple transluminal gateway technique, a 24-Fr percutaneous catheter was inserted for irrigation and drainage (*Fig. 4*). In consultation with radiology, the percutaneous catheter was positioned in the dependent portion of the necrotic collection to optimize drainage under gravity.

Suboptimal response

If the response was suboptimal, and there was a lack of clinical or radiological improvement (less than 50 per cent decrease in size on abdominopelvic CT), percutaneous necrosectomy was performed (*Fig. 5*; *Video S2*, supporting information). The percutaneous catheter tract was dilated to 48 Fr using Savary dilators and a fully covered self-expanding oesophageal metal stent was placed to

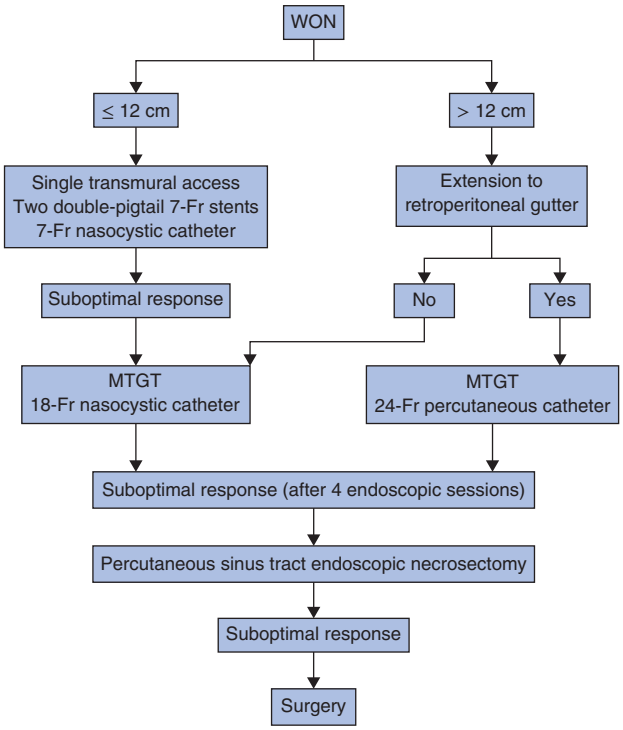

Fig. 1 Algorithmic approach to the endoscopic management of walled-off necrosis (WON). A suboptimal response was defined clinically as persistence of symptoms, organ failure, systemic inflammatory response syndrome or sepsis; and radiologically as a decrease in WON size of less than 50 per cent on CT of the abdomen/pelvis. MTGT, multiple transluminal gateway technique

provide access to the necrotic cavity for debridement. The proximal end of the stent was inserted into the walled-off necrosis cavity and the distal end was positioned at the anterior abdominal wall. If the collection was 20 cm or less from the anterior abdominal wall, debridement was undertaken using the gastroscope as a light source with a combination of laparoscopic and endoscopic accessories. If the distance was greater than 20 cm and there was extensive necrosis tracking to the flanks, debridement was performed primarily using the endoscope alone. Debridement was continued until at least 75 per cent of the cavity had been cleared and had developed red granulation tissue.

Treatment failure

A maximum of four interventions were performed per patient. If there was no clinical or radiological improvement, a consult was obtained to pursue surgical necrosectomy as a definitive treatment. Emergency surgical consultation was obtained if a major adverse event occurred at endoscopy and for acute clinical deterioration at any phase of the treatment.

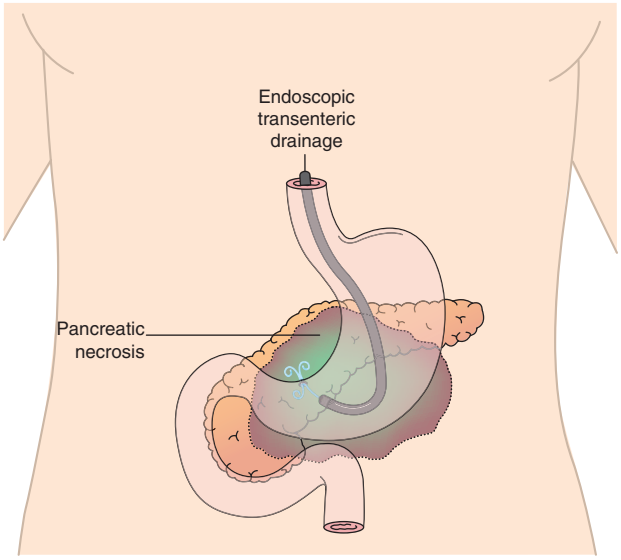

Fig. 2 Conventional transmural drainage by placement of stent and nasocystic catheter for management of walled-off necrosis measuring 12 cm or less in size

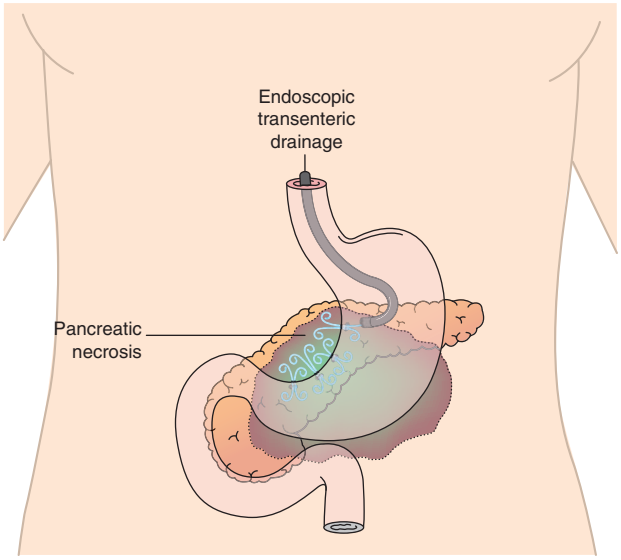

Fig. 3 Endoscopic treatment of walled-off necrosis measuring more than 12 cm in size using the multiple transluminal gateway technique

Percutaneous/nasocystic catheter management

The catheter was flushed with 250 ml normal saline plus 80–120 mg gentamicin every 4–6 h, with frequent repositioning of the patient to facilitate irrigation and drainage of the necrotic contents. Additional 24-Fr percutaneous catheters were inserted in patients with loculated or multifocal walled-off necrosis that was not accessible for endoscopic drainage.

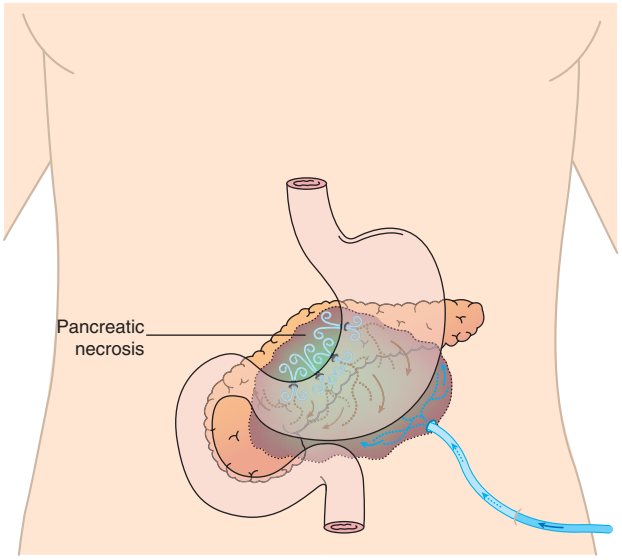

Fig. 4 Endoscopic treatment of walled-off necrosis measuring more than 12 cm in size with extension to flanks using the multiple transluminal gateway technique and placement of large-bore percutaneous catheters

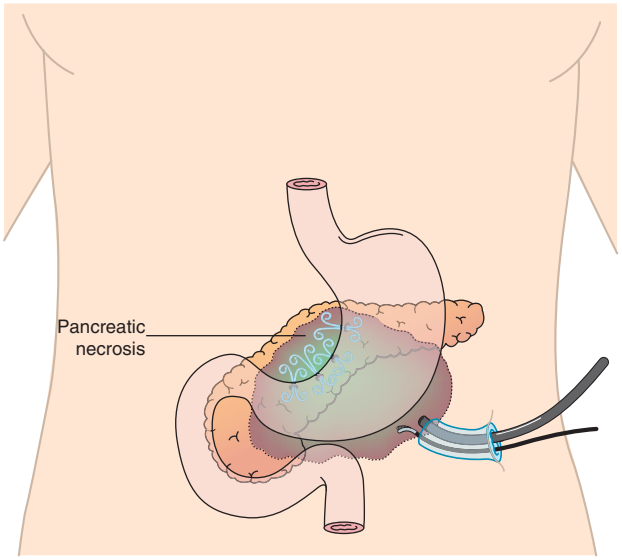

Fig. 5 Percutaneous necrosectomy following suboptimal response to endoscopic treatment of walled-off necrosis

Follow-up treatment in both groups

Three days after the initial intervention, if the walled-off necrosis had decreased in size by 50 per cent or more in association with clinical improvement, the nasocystic and/or percutaneous catheters were removed and the patient was discharged from hospital. If there was a

suboptimal clinical or radiological response (less than 50 per cent decrease in size of the walled-off necrosis on abdominopelvic CT) to the initial intervention, endoscopic intervention was continued as outlined above.

All patients had outpatient abdominopelvic CT at 8 weeks. If the walled-off necrosis had resolved and the main pancreatic duct was intact, the transmural stents were removed. Two transmural stents were left *in situ* indefinitely in patients with disconnected pancreatic duct syndrome to reduce the risk of recurrent collections[22,23]. Enteral nutrition was discontinued at follow-up in all patients, and those with persistent symptomatic walled-off necrosis were referred for surgery.

Definitions

Treatment success was defined as reduction in walled-off necrosis size to 2 cm or less on follow-up abdominopelvic CT at 8 weeks, with symptom resolution. Treatment failure was defined as persistence of walled-off necrosis on follow-up CT at 8 weeks, need for surgical necrosectomy or disease-specific death. 'Hybrid' treatment was defined as the multiple transluminal gateway technique and/or percutaneous necrosectomy techniques.

The primary outcome measure was treatment success, which was compared between the two management approaches (conventional *versus* algorithmic). Predictors of treatment success were identified.

Statistical analysis

Data sets were compiled using Microsoft® Excel (Microsoft Corporation, Richmond, Washington, USA). Patient characteristics, features of walled-off necrosis, procedural details and treatment outcomes were compared between the two treatment groups. These variables were also compared according to treatment success in order to anticipate which variables may be associated with treatment success in logistic regression. Continuous variables were summarized as mean(s.d.) and median (i.q.r. and range) values, and compared using the Wilcoxon rank sum test. The χ^2 test and Fisher's exact test were used for analysis of categorical data.

Multiple logistic regression and reverse stepwise multivariable logistic regression analyses were then performed to identify variables associated with treatment success. The outcome variable of treatment success was taken as a binary variable (treatment success or failure). Predictor variables that were either clinically relevant or statistically significant in univariable analysis were included in the multivariable analysis. $P < 0{\cdot}050$ was considered statistically significant and all statistical analyses were done using Stata® 13 (StataCorp LP, College Station, Texas, USA).

Table 1 Overall demographic and clinical characteristics (100 patients)

	No. of patients*
Age (years)	
Mean(s.d.)	52·0(16·5)
Median (i.q.r.)	53 (41–64)
Range	11–84
Sex ratio (M : F)	63 : 37
Race	
Caucasian	76 (76·0)
African–American	20 (20·0)
Asian	2 (2·0)
Hispanic	2 (2·0)
Type of pancreatitis	
Acute	61 (61·0)
Chronic	39 (39·0)
Aetiology of pancreatitis	
Alcohol	31 (31·0)
Idiopathic	36 (36·0)
Gallstones	17 (17·0)
Hypertriglyceridaemia	4 (4·0)
Post-ERCP	2 (2·0)
After surgery/trauma	7 (7·0)
Drug-induced	2 (2·0)
Pancreas divisum	1 (1·0)
Serum white cell count ($\times 10^9$/l)	
Mean(s.d.)	14·2(6·6)
Median (i.q.r.)	14·5 (8·9–18·2)
Range	1·0–40·8
Serum albumin (g/dl)	
Mean(s.d)	2·5(0·7)
Median (i.q.r.)	2·4 (2·0–3·0)
Range	1·1–4·1
Duration of WON (weeks)	
Mean(s.d.)	8·7(7·5)
Median (i.q.r.)	6 (5–10)
Range	2–50
Location of WON	
Head	15 (15·0)
Uncinate	1 (1·0)
Body	70 (70·0)
Tail	14 (14·0)
Size of WON – long axis (cm)	
Mean(s.d.)	11·4(4·6)
Median (i.q.r.)	11·0 (8·0–13·8)
Range	3·8–33·0

*With percentages in parentheses unless indicated otherwise. ERCP, endoscopic retrograde cholangiopancreatography; WON, walled-off necrosis.

Results

One hundred patients were enrolled, 47 in group 1 and 53 in group 2. The mean age was 52·0 years; 63 (63·0 per cent) were men and 76 (76·0 per cent) Caucasian. The aetiology

Table 2 Demographic and clinical characteristics and procedure details according to treatment approach

	Conventional treatment ($n = 47$)	Algorithmic treatment ($n = 53$)	P‡
Age (years)			
Mean(s.d.)	51·0(14·3)	52·9(18·3)	
Median (i.q.r.)	52 (41–61)	55 (39–64)	0·437§
Range	11–79	11–84	
Sex ratio (M : F)	36 : 11	27 : 26	0·008
Race			0·007
Caucasian	30 (64)	46 (87)	
Non-Caucasian	17 (36)	7 (13)	
Type of pancreatitis			0·132
Acute	25 (53)	36 (68)	
Chronic	22 (47)	17 (32)	
Aetiology of pancreatitis			0·055
Alcohol	19 (40)	12 (23)	
Other	28 (60)	41 (77)	
Serum white cell count ($\times 10^9$/l)			
Mean(s.d.)	14·2(5·8)	14·2(7·3)	
Median (i.q.r.)	14·3 (9·1–18·5)	14·5 (8·0–18·0)	0·756§
Range	5·4–29·9	1·0–40·8	
Serum albumin (g/dl)			
Mean(s.d.)	2·3(0·7)	2·6(0·7)	
Median (i.q.r.)	2·1 (1·8–2·9)	2·7 (2·0–3·0)	0·058§
Range	1·1–4·1	1·5–4·0	
Duration of WON (weeks)			
Mean(s.d.)	8·8(5·7)	8·6(8·8)	
Median (i.q.r.)	6 (5–11)	5 (4–10)	0·072§
Range	3–34	2–50	
Location of WON			
Head/uncinate	11 (23)	5 (9)	0·099¶
Body/tail	36 (77)	48 (91)	
Size of WON – long axis (cm)			
Mean(s.d.)	11·4(3·9)	11·5(5·2)	
Median (i.q.r.)	11·0 (9·0–13·0)	11·0 (8·0–14·0)	0·700§
Range	4·5–22·0	3·8–33·0	
Multiple WONs	5 (11)	8 (15)	0·564¶
Type of endoscopic drainage			< 0·001¶
EUS	30 (64)	51 (96)	
CTD	17 (36)	2 (4)	
Route of drainage			0·218¶
Transoesophageal/gastric	39 (83)	49 (92)	
Transduodenal	8 (17)	4 (8)	
Luminal compression present	22 (47)	25 (47)	0·971
PD stent placed	7 (15)	9 (17)	0·999¶
Hybrid treatment*	5 (11)	23 (43)	< 0·001
Direct endoscopic necrosectomy	4 (9)	1 (2)	0·184¶
Enteral nutrition	30 (64)	24 (45)	0·063
Treatment success	28 (60)	48 (91)	< 0·001
No. of interventions			
Mean(s.d.)	1·4(0·6)	1·4(0·7)	
Median (i.q.r.)	1 (1–2)	1 (1–1)	0·535§
Range	1–3	1–4	
Duration of postprocedure hospital stay (days)†			
Mean(s.d.)	11·8(12·4)	8·7(11·4)	
Median (i.q.r.)	5 (3–17)	4 (3–7)	0·155§
Range	0–45	1–62	

Values in percentages are parentheses unless indicated otherwise. *Multiple transluminal gateway technique with or without percutaneous necrosectomy. †Calculated from the date of initial procedure to the date of discharge. WON, walled-off necrosis; EUS, endoscopic ultrasonography; CTD, conventional transmural drainage; PD, pancreatic duct. ‡χ^2 test, except §Wilcoxon rank sum test and ¶Fisher's exact test.

Table 3 Multivariable analysis of factors associated with treatment success

	Odds ratio	*P*
Multiple logistic regression analysis		
Age (≤ 50 *versus* > 50 years)	1·11 (0·35, 3·53)	0·862
Sex (F *versus* M)	0·57 (0·16, 2·12)	0·406
Race (Caucasian *versus* non-Caucasian)	0·57 (0·14, 2·42)	0·447
Serum white cell count: (≤ 12 *versus* > 12 × 10^9/l)	1·67 (0·45, 6·21)	0·442
Serum albumin (> 2·5 *versus* ≤ 2·5 g/dl)	1·05 (0·29, 3·77)	0·940
Aetiology of WON (not alcohol *versus* alcohol)	1·69 (0·44, 6·46)	0·441
Duration of WON (≤ 4 *versus* > 4 weeks)	1·38 (0·29, 6·64)	0·689
Location of WON (body/tail *versus* head/uncinate)	1·26 (0·28, 5·65)	0·767
Size of WON (≤ 10·0 *versus* > 10·0 cm)	0·92 (0·22, 3·89)	0·909
Single *versus* multiple WON	0·87 (0·14, 5·36)	0·877
Type of endoscopic drainage (EUS *versus* CTD)	0·21 (0·03, 1·32)	0·096
Luminal compression (present *versus* absent at endoscopy)	0·30 (0·05, 1·73)	0·176
PD stent placed (yes *versus* no)	2·01 (0·33, 12·33)	0·453
Enteral nutrition (yes *versus* no)	0·93 (0·28, 3·07)	0·908
No. of interventions (1 *versus* 2–4)	2·00 (0·58, 6·90)	0·271
Treatment (algorithmic *versus* conventional)	14·48 (2·94, 71·46)	0·001
Reverse stepwise multivariable logistic regression analysis		
Treatment (algorithmic *versus* conventional)	6·51 (2·19, 19·37)	0·001

Values in parentheses are 95 per cent confidence intervals. WON, walled-off necrosis; EUS, endoscopic ultrasonography; CTD, conventional transmural drainage; PD, pancreatic duct.

of pancreatitis was idiopathic in 36 (36·0 per cent), alcohol in 31 (31·0 per cent) and gallstones in 17 (17·0 per cent). The overall clinical characteristics, walled-off necrosis features and laboratory parameters of the study cohort are shown in *Table 1*. Except for sex distribution and race, there was no difference in patient demographics, clinical or walled-off necrosis characteristics and laboratory parameters between the two groups (*Table 2*). The median size of the walled-off necrosis collection was 11·0 cm.

Procedure details

Access and drainage of the collection was transgastric in 88 patients (88·0 per cent), and percutaneous endoscopic gastrojejunostomy feeding tubes were inserted in 54 (54·0 per cent) for enteral nutrition (*Table 2*). A disconnected main pancreatic duct was identified in more than 60·0 per cent of patients and a pancreatic duct stent bridging the leak was placed in 16 patients, with no difference between the groups. A bridging pancreatic duct stent was not placed in others for the following reasons: inability to bridge the disconnected main pancreatic duct (63), gastric outlet obstruction (6), pancreatic duct strictures or stones (5) and a normal pancreatogram (10).

Direct endoscopic necrosectomy was undertaken in four patients in the early group and only one after introduction of the algorithm. The latter patient had a spontaneous fistula in the duodenal bulb, and the fistulous tract was accessed for endoscopic debridement and stent placement.

Treatment outcomes

Endoscopic treatment was successful in 76 patients (76·0 per cent) overall. The treatment success rate was significantly higher in the algorithmic treatment group: 48 (91 per cent) *versus* 28 (60 per cent) ($P < 0·001$) (*Table S1* and *Fig. S1*, supporting information). Endoscopic treatment failed in 24 patients (group 1, 19; group 2, 5) with persistence of walled-off necrosis in 17 (group 1, 13; group 2, 4), postprocedural walled-off necrosis infection in five (all group 1) and perforation in two patients (1 in each group). Two of the 24 patients with endoscopic treatment failures died from multiple organ failure and 22 proceeded to surgery. Of these, 20 had a good clinical outcome and two died from postoperative adverse events. At a median follow-up of 413 days, five patients had developed a recurrent pancreatic fluid collection, of whom three underwent repeat endoscopic drainage and two were managed surgically.

Hybrid technique

A hybrid technique was used in five patients in group 1 (multiple transluminal gateway technique plus 18-Fr nasocystic catheter) and 23 patients in group 2 (multiple transluminal gateway technique in combination with an 18-Fr nasocystic catheter, 10 patients; 24-Fr percutaneous catheters, 13 patients; and/or percutaneous necrosectomy, 7 patients) (*Table 2*). Treatment was successful in 26 of the 28 patients treated by a hybrid approach. Endoscopic treatment failed in two patients (with persistent sepsis and perforation) and both subsequently underwent surgery with good clinical outcome.

Predictors of treatment success

On multiple logistic regression analysis, management by the algorithmic approach (odds ratio (OR) 14·48, 95 per cent c.i. 2·94 to 71·46; $P = 0·001$) was the only factor

independently associated with treatment success after adjustment for patient demographics, laboratory parameters, walled-off necrosis characteristics, enteral nutrition, pancreatic duct stent placement and modality used for walled-off necrosis drainage (*Table 3*). The algorithmic approach remained significant as the predictor of treatment success on reverse stepwise multivariable logistic regression analysis (OR 6·51, 95 per cent c.i. 2·19 to 19·37; $P = 0·001$).

Adverse events

There were 12 procedural adverse events: perforations in two patients (1 in each group), infections in six (group 1, 5; group 2, 1), bleeding in one (group 1) and stent migration in three (group 1, 1; group 2, 2). Both perforations occurred when walled-off necrosis arose from the uncinate process following creation of the transmural tract. As the collection drained rapidly, the walled-off necrosis collapsed towards the uncinate and separated from the gastric wall, resulting in a free perforation. Surgery was successful in both patients. One patient in group 1 developed postprocedure bleeding at the site of transmural stenting and this was managed by coil embolization. Stent migration resulted in small bowel obstruction in two patients (1 managed surgically and 1 conservatively). One patient had stent migration into the walled-off necrosis, which could not be retrieved endoscopically and was managed conservatively.

Discussion

This study shows that a structured, stepwise approach to the size and extent of walled-off necrosis yields improved clinical outcomes. Endoscopic techniques to treat walled-off necrosis have evolved over the past decade. Treatment with transmural stents and drainage catheters yields suboptimal outcomes, and often necessitates direct endoscopic necrosectomy[19,20]. However, endoscopic necrosectomy is associated with high procedure-related morbidity and mortality rates, is labour-intensive, resource-consuming, and devices specifically designed for necrosectomy are lacking. In the multicentre GEPARD study[15], the procedure-related adverse event rate was 26 per cent, with 2·1 per cent mortality. Furthermore, perforation occurred in 5·3 per cent, bleeding in 14 per cent and clinically significant air embolism in two patients. There is growing evidence that aggressive irrigation and drainage of the walled-off necrosis cavity yields comparable or better outcomes, while avoiding the adverse events of direct endoscopic necrosectomy[24]. In a study that compared a minimally invasive step-up approach with open surgical necrosectomy[6], one-third of patients managed initially by percutaneous drainage did not require subsequent surgical interventions. Therefore, there are advantages to a less invasive approach[21], and now open surgical necrosectomy is rarely performed if minimally invasive techniques are available.

The present study demonstrates that improved outcomes can be achieved by tailoring the endoscopic approach to the specific characteristics of each collection. Procedure-related infection and persistence of walled-off necrosis were the most common causes of treatment failure in the conventional treatment group. In contrast, the algorithmic approach resulted in a high treatment success rate and less procedure-related morbidity. This is likely the result of a combination of improved drainage with the multiple transluminal gateway technique, increased irrigation (through both endoscopic and percutaneous catheters) and early collaboration with pancreatic surgeons to perform minimally invasive percutaneous debridement when indicated. Although the efficacy of these individual stepwise interventions has not been studied in a randomized setting, the data suggest that the stepwise approach improves outcomes.

This study has several limitations. First, reported results derive from centres with advanced expertise in pancreatic disorders. The multidisciplinary care delivered by endoscopists, interventional radiologists, pancreatic surgeons and intensivists may be unique, and represents teamwork that is institution-specific. Likewise, some aspects of the treatment, such as the antibiotic schedule, use of ERCP to investigate for pancreatic ductal integrity, dilatation of the transmural tract to less than 15 mm, creation of multiple internal conduits for drainage and lavage of necrotic contents using antibiotic mixed with saline, were institution-specific and not evidence-based, thereby limiting the applicability of this practice to other centres. In addition, walled-off necrosis was secondary to gallstones in only 17·0 per cent of patients and the aetiology was unknown in one-third of the study cohort. Walled-off necrosis was detected in the setting of chronic pancreatitis in 39·0 per cent of patients, suggesting a referral bias, which limits the applicability of the study findings to all patients with walled-off necrosis. Second, the algorithm outlined in this study evolved over time and requires external validation. Some facets, such as the decision to proceed with placement of percutaneous *versus* nasocystic catheters, were collaborative. In the authors' experience, percutaneous catheters allowed better access and irrigation than nasocystic catheters when walled-off necrosis extended into the flanks. When percutaneous necrosectomy was later required, the shortest percutaneous distance from the

skin to the cavity was preferred. Percutaneous endoscopic necrosectomy is a useful technique, particularly in obese patients, in whom laparoscopically assisted necrosectomy is challenging. Third, a proportion of patients with walled-off necrosis can be managed without intervention. The present results suggest, however, that this algorithmic approach may improve treatment success should intervention be required. Fourth, it is uncommon for walled-off necrosis smaller than 12 cm to tract to the flanks, and this was not encountered here. However, it must be noted that the cut-off size of 12 cm chosen in this study was arbitrary; larger collections that are completely liquefied can resolve with simple drainage measures, whereas some smaller collections with large amounts of necrosis may require multiple endoscopic or adjunctive interventions[25,26]. Fifth, as the patients were treated over a 10-year interval, their clinical management may have varied over time. Improvement in the quality of imaging and revision of the Atlanta classification[3] may have facilitated more accurate categorization of pancreatic fluid collections and timely delivery of effective treatment, which evolved with the growing experience and expertise of the endoscopy team. Sixth, MRI, which is considered superior to CT for the evaluation of walled-off necrosis, was not performed in all patients in this study. Finally, the findings of this study pertain to patients treated primarily by endoscopic techniques and these results may not be applicable to the entire spectrum of patients with walled-off necrosis requiring other forms of treatment. The study did not compare the long-term outcomes between the two treatment approaches, and long-term data are required before definitive conclusions can be established.

Acknowledgements

J.Y.B. and B.A.H. contributed equally to this manuscript. S.V. and R.H.H. are Consultants for Boston Scientific Corporation and Olympus America Inc.
Disclosure: The authors declare no other conflict of interest.

References

1 Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; **144**: 1252–1261.
2 Beger HG, Rau B, Mayer J, Pralle U. Natural course of acute pancreatitis. *World J Surg* 1997; **21**: 130–135.
3 Banks PA, Bollen TL, Dervenis C, Goozen HG, Johnson CD, Sarr MG *et al.*; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102–111.
4 Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13**: e1–e15.
5 Cirocci R, Trastulli S, Desiderio J, Boselli C, Parisi A, Noya G *et al.* Minimally invasive necrosectomy *versus* conventional surgery in the treatment of infected pancreatic necrosis: a systematic review and a meta-analysis of comparative studies. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 8–20.
6 van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boemeester MA, Dejong CH *et al.*; Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010; **362**: 1491–1502.
7 van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM *et al.*; Dutch Pancreatitis Study Group. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2013; **141**: 1254–1263.
8 Raraty MG, Halloran CM, Dodd S, Ghaneh P, Connor S, Evan J *et al.* Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. *Ann Surg* 2010; **251**: 787–793.
9 Varadarajulu S, Phadnis MA, Christein JD, Wilcox CM. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic walled-off pancreatic necrosis. *Gastrointest Endosc* 2011; **74**: 74–80.
10 Gluck M, Ross A, Irani S, Lin O, Gan SI, Fotoohi M *et al.* Dual modality drainage for symptomatic walled-off pancreatic necrosis reduces length of hospitalization, radiological procedures, and number of endoscopies compared to standard percutaneous drainage. *J Gastrointest Surg* 2012; **16**: 248–257.
11 Gardner TB, Coelho-Prabhu N, Gordon SR, Gelrud A, Maple JT, Papachristou GI *et al.* Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multi-center U.S. series. *Gastrointest Endosc* 2011; **73**: 718–726.
12 Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL *et al.*; Dutch Pancreatitis Study Group. Endoscopic transgastric *vs* surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012; **307**: 1053–1061.
13 Sarkaria S, Sethi A, Rondon C, Lieberman M, Srinivasan I, Weaver K *et al.* Pancreatic necrosectomy using covered esophageal stents: a novel approach. *J Clin Gastroenterol* 2014; **48**: 145–152.
14 Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG *et al.*; International Association of Pancreatology. IAP Guidelines for the surgical management of acute pancreatitis. *Pancreatology* 2002; **2**: 565–573.
15 Seifert H, Biermer M, Schmitt W, Jürgensen C, Will U, Gerlach R *et al.* Transluminal endoscopic necrosectomy after acute pancreatitis: a multicenter study with long-term follow-up (the GEPARD study). *Gut* 2009; **58**: 1260–1266.

16 Ross A, Gluck M, Irani S, Hauptmann E, Fotoohi M, Siegal J *et al.* Combined endoscopic and percutaneous drainage of organized pancreatic necrosis. *Gastrointest Endosc* 2010; **71**: 79–84.
17 Becker V, Huber W, Meining A, Prinz C, Umgelter A, Ludwig L *et al.* Infected necrosis in severe pancreatitis – combined nonsurgical multi-drainage with directed transabdominal high-volume lavage in critically ill patients. *Pancreatology* 2009; **9**: 280–286.
18 Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013; **145**: 583–590.
19 Varadarajulu S, Bang JY, Phadnis MA, Christein JD, Wilcox CM. Endoscopic transmural drainage of peripancreatic fluid collections: outcomes and predictors of success in 211 consecutive patients. *J Gastrointest Surg* 2011; **15**: 2080–2088.
20 Baron TH, Harewood GC, Morgan DE, Yates MR. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. *Gastrointest Endosc* 2002; **56**: 7–17.
21 Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology* 2013; **144**: 333–340.
22 Varadarajulu S, Wilcox CM. Endoscopic placement of permanent indwelling transmural stents in disconnected pancreatic duct syndrome: does benefit outweigh the risks? *Gastrointest Endosc* 2011; **74**: 1408–1412.
23 Arvanitakis M, Delhaye M, Bali MA, Matos C, De Maertelaer V, Le Moine O *et al.* Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. *Gastrointest Endosc* 2007; **65**: 609–619.
24 Ross AS, Irani S, Gan SI, Rocha F, Siegal J, Fotoohi M *et al.* Dual-modality drainage of infected and symptomatic walled-off pancreatic necrosis: long-term clinical outcomes. *Gastrointest Endosc* 2014; **79**: 929–935.
25 Freeman ML, Werner J, van Santvoort HC, Baron TH, Besselink MG, Windsor JA *et al.*; International Multidisciplinary Panel of Speakers and Moderators. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. *Pancreas* 2012; **41**: 1176–1194.
26 da Costa DW, Boerma D, van Santvoort HC, Horvath KD, Werner J, Carter CR *et al.* Staged multidisciplinary step-up management for necrotizing pancreatitis. *Br J Surg* 2014; **101**: e65–e79.

Supporting information

Additional supporting information may be found in the online version of this article:

Video S1 Multiple transluminal gateway technique for the management of walled-off necrosis (wmv file)

Video S2 Stepwise management of a large haemorrhagic walled-off necrosis involved insertion of a large-bore percutaneous drain followed by endoscopic ultrasonography and internal drainage using the multiple transluminal gateway technique. Percutaneous necrosectomy was later performed, with excellent clinical outcome (wmv file)

Fig. S1 Comparison of success rate of conventional and algorithmic treatments for patients with walled-off necrosis treated over 10 years (Word document)

Table S1 Comparison of patient characteristics and procedure details according to treatment outcome (Word document)