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Original Article

Disconnected pancreatic duct syndrome predicts failure of percutaneous therapy in necrotizing pancreatitis☆

Thomas K. Maatman, Sarakshi Mahajan, Alexandra M. Roch, Eugene P. Ceppa, Michael G. House, Attila Nakeeb, C. Max Schmidt, Nicholas J. Zyromski*

Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

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ABSTRACT

Background/objectives: Minimally invasive approaches, such as percutaneous drainage (PD), are increasingly utilized as initial treatment in necrotizing pancreatitis (NP) requiring intervention. Predictors of success of PD as definitive treatment are lacking. Our aim was to assess the application, predictors of success, and natural history of PD in NP. We hypothesized that necrosis morphology patterns and disconnected pancreatic duct syndrome (DPDS) may predict the ability of PD to provide definitive therapy.

Methods: 714 NP patients were treated from 2005 to 2018. Patients achieving disease resolution with PD alone (PD) were compared to those requiring an escalation in intervention (Step). Outcomes were compared between groups using independent samples t-test, Fisher's exact test, and Pearson's correlation, as appropriate. $P < 0.05$ was accepted as statistically significant.

Results: 115 patients were initially managed with PD (42 PD, 73 Step). No difference in necrosis morphology was seen between the two groups. The PD group underwent significantly more repeat percutaneous interventions (PD, 3.2; Step, 2.0; $P = 0.0006$) including additional drain placement and drain upsize/reposition procedures. Patients with DPDS were more likely to require an escalation in intervention (odds ratio, 3.4; 95% confidence interval, 1.5–7.6; $P = 0.003$). The mean number of months to NP resolution was similar (PD, 5.7; Step, 5.8; $P = 0.9$). Mortality was similar (PD, 7%; Step 14%, $P = 0.3$).

Conclusions: Necrosis morphology in and of itself does not reliably predict successful definitive treatment by percutaneous drainage. However, patients with disconnected pancreatic duct syndrome were less likely to have definitive resolution with PD alone.

Introduction

Necrotizing pancreatitis (NP) develops in up to 20% of patients with acute pancreatitis [1–3]. The natural history of NP and associated acute necrotic collections (ANC) or walled-off necrosis (WON) is becoming defined more clearly. In patients developing an ANC, as many as one-third will resolve without intervention at four weeks [4,5]. As these ANC mature to WON, intervention is required in 40–63% of patients [4,5].

Over the last decade, the management of NP patients with WON has evolved dramatically. Historically, open pancreatic debridement (OPD) was the gold standard of therapy [6,7]. However, over the last decade it has become apparent that patients requiring intervention benefit from minimally invasive approaches as a first step in treatment (i.e. percutaneous drainage or endoscopic drainage/debridement) [8–10]. As this approach has been applied more widely, it has become clear that up to one-third of patients requiring intervention will achieve disease resolution simply with percutaneous drainage alone [9,11,12].

Currently no reliable means exist with which to predict those patients who resolve with percutaneous drainage (PD) alone and those patients who will require a "step-up" to more definitive management. Additionally, no consensus exists regarding the timing from first PD to the next intervention, be it further PD or escalation to a different treatment modality. The ability to reliably

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* Corresponding author. Department of Surgery, Indiana University School of Medicine, 545 Barnhill Dr, EH 519, Indianapolis, IN, 46202.
E-mail address: nzyromsk@iupui.edu (N.J. Zyromski).

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predict those patients likely to succeed would allow for the highly individualized care required of NP patients. Patients deemed "high-risk" for failure could be streamlined through the treatment algorithm. Those patients with a high likelihood of success may be managed more expectantly, avoiding unnecessary interventions.

Multiple methods of describing necrosis extent and location exist. In 1985, Balthazar et al. described a technique evaluating the size, contour, and density of the pancreas as well as peripancreatic abnormalities that became the Balthazar grading system [13]. Expanding on this paradigm, the computed tomography severity index (CTSI) elaborates on the Balthazar grade by including the percent of glandular necrosis (none, <30%, 30–50%, >50%) [14]. Anatomically, glandular necrosis can include necrosis involving the head, neck, uncinate, body, and/or tail. Similarly, extrapancreatic necrosis can be anatomically classified by location - the lesser sac, paracolic gutters, or the root of the small bowel mesentery.

We hypothesized that specific anatomical features of necrotizing pancreatitis may predict definitive treatment by percutaneous drainage alone. Therefore, the aim of this study was to analyze the impact of specific pancreatic necrosis morphology and the presence of disconnected pancreatic duct syndrome on success of percutaneous drainage.

Methods

An institutional prospectively collected NP database was reviewed. This database includes all NP patients treated at Indiana University Health University Hospital (IU-UH) starting in 2005 and is approved by the Institutional Review Board (IRB). A total of 714 NP patients were treated between 2005 and 2018. Acute pancreatitis and severe acute pancreatitis were defined according to the revised Atlanta classification [3]. Onset of pancreatitis was defined as the date of symptom onset. Necrosis was identified as a lack of pancreatic parenchymal enhancement and/or findings of peripancreatic necrosis such as acute necrotic collection (ANC) or walled off necrosis (WON) on contrast enhanced cross sectional imaging (either computed tomography or magnetic resonance imaging) [3]. Institutional management of NP patients mirrors that of the International Association of Pancreatology and American Pancreatic Association guidelines [15]. Intervention on pancreatic necrosis is ideally delayed >4 weeks from onset of disease; however, this is not always possible as infected necrosis with clinical deterioration prompts intervention earlier than planned.

Those patients that underwent PD as the first therapy for NP requiring intervention were identified. During the study period, institutional practice began with percutaneous drainage when infected necrosis caused clinical deterioration. The decision of timing and type of intervention is made on an individual patient basis and with agreement among a multidisciplinary team experienced in the management of NP (including pancreas surgeons, interventional gastroenterologists, medical pancreatologists, and interventional radiologists). The size of the initial drain placement is at the discretion of the interventional radiologist performing the procedure. Following placement of PD, drains are routinely flushed with 10–50 mL of normal saline every six to eight hours to maintain patency and assist in freeing loose necrosis. The institutional protocol following initial drain placement is proactive and utilizes upsizing, repositioning, and placement of additional PD in the event clinical or radiographic improvement is not seen within a short interval after initial drain placement. Each individual patient's clinical course was evaluated. Patients dying prior to disease resolution were included in the analysis according to the intention-to-treat principle. Patients were classified into two groups: patients in which percutaneous drainage alone achieved disease resolution (PD) and patients requiring escalation of care according to the "step-up" approach (Step). Cross sectional imaging immediately prior to first percutaneous drain placement was reviewed by a single, experienced pancreatologist. The presence or absence of necrosis in the following six anatomic fields was recorded: pancreatic parenchymal head/neck, pancreatic parenchymal body/tail, peripancreatic lesser sac, peripancreatic left paracolic gutter, peripancreatic right paracolic gutter, and peripancreatic root of the small bowel mesentery, Fig. 1. Multi-field necrosis was defined as the presence of more than two of these patterns. Disconnected pancreatic duct syndrome (DPDS) was diagnosed when necrosis involved at least 2 cm of pancreas with viable upstream (left-sided) pancreatic parenchyma and extravasation of contrast or total cutoff of the main pancreatic duct on cholangiopancreatography [16,17]. All suspected cases of DPDS were confirmed with endoscopic retrograde pancreatography or magnetic resonance pancreatography.

Definitive management with percutaneous drainage alone (PD) was achieved if the patient met all of the following criteria: no additional modality of intervention (endoscopic, surgical) following PD, clinical and radiographic resolution of necrosis (absent drain output in the setting of resolved collection on cross sectional imaging), and no repeat intervention or evidence of recurrent collection on follow-up imaging three months following the removal of all percutaneous drains. Patients remained in the PD group if only percutaneous interventions were performed, including additional PD placement, PD upsizing, and/or PD repositioning. Patients requiring escalation of care following percutaneous drainage to endoscopic drainage/debridement, surgical debridement, or a combination, were considered failed management with PD and included in the "step-up" group (Step). Minimally invasive surgical necrosectomy includes laparoscopic debridement, transgastric debridement, sinus tract necrosectomy, and video-assisted retroperitoneal debridement.

Clinical factors during the course of the disease and individual outcomes following initial drain placement were evaluated and recorded, including: repeat drainage procedures (drain repositioning, drain upsizing, drain replacement, and/or additional drain placement), drain size (initial, maximum, and final size), presence of DPDS, time to "step-up", "step-up" procedures, time to resolution of disease, and requirement of late operation.

Descriptive statistics included number with percentage, mean with standard deviation (SD), and median with range. As appropriate, Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. Mean values were compared using independent samples *t*-test. Odds ratios (OR) are reported with 95% confidence intervals (CI). A P-value < 0.05 was considered significant.

Results

Between 2005 and 2018, a total of 714 NP patients were treated. Definitive pancreatic necrosis management of all 714 NP patients is shown in Fig. 2. The mortality of all NP patients was 9% (n = 65). Of the 714 patients, 115 patients (16%) underwent placement of a percutaneous drain as the first intervention in NP requiring treatment; 42 patients (37%) required PD alone (PD) and 73 patients (63%) required an escalation to more invasive intervention (Step). This relatively small subgroup reflects both an evolution in our clinical practice [19] and the quaternary pancreas practice where about 80% of NP patients are initially treated elsewhere prior to transfer to IU-UH.

In all patients undergoing PD as the initial management of necrosis, initial drain placement occurred a mean of 32.7 days (SD, 26.6) following NP onset. The mean time to step-up was 29.4 days (SD, 24.6) following initial drain placement. Step-up included open

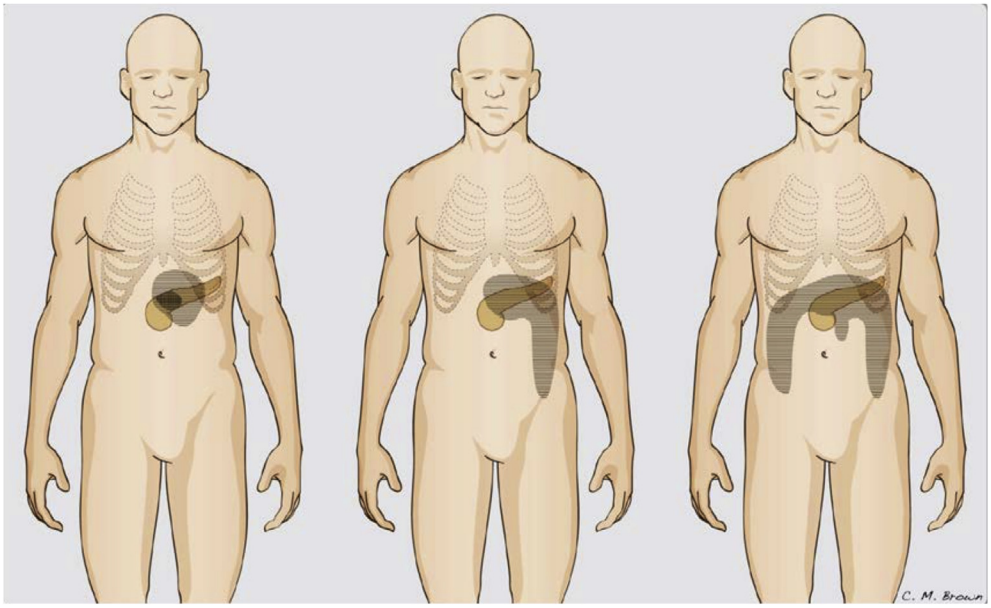

Fig. 1. Illustration of typical necrosis patterns. Left – glandular necrosis involving the neck of the pancreas with associated peripancreatic necrosis isolated to the lesser sac; Middle – peripancreatic necrosis in the lesser sac and left paracolic gutter; Right – multifield peripancreatic necrosis including the lesser sac, left and right paracolic gutters, and necrosis tracking down the root of the small bowel mesentery. Reprinted from "Transgastric Pancreatic Necrosectomy: How I Do It," by NJ Zyromski, A Nakeeb, MG House, and AL Jester, 2016 [18].

pancreatic debridement (n = 52), minimally invasive surgical necrosectomy (n = 15), and endoscopic necrosectomy (n = 6). The number of percutaneous procedures prior to resolution (PD) or prior to step-up (Step) is shown in Fig. 3. The timing of subsequent percutaneous interventions did not differ between groups, Fig. 4.

A comparison of necrosis morphology between groups is shown in Table 1. When considered individually, no pattern of glandular necrosis or peripancreatic necrosis predicted definitive resolution of necrosis with PD alone. Likewise, neither the presence of multifield necrosis, nor the number of fields of necrosis predicted resolution with PD. The mean number of involved fields per patient was similar between groups and morphologic patterns between the two groups were similar.

No difference was seen in the timing of the first drain placement between groups, Table 2. Additionally, no difference was seen in drain size between the two groups, including initial drain size, maximum drain size, and final drain size. The only clinical factor associated with failure of PD management was the presence of disconnected pancreatic duct syndrome (DPDS). In patients with necrosis resolving with percutaneous drainage alone the incidence of DPDS was 29% (n = 12) compared to 58% (n = 42) in those patients requiring an escalation in therapy, $P = 0.003$. The presence of DPDS in the setting of NP requiring intervention constituted a 3.4-fold (95% CI, 1.5–7.6) increased risk of failure of management with PD alone, $P = 0.003$.

Clinical outcomes are shown in Table 3. Those patients resolving with PD alone (PD) underwent more total repeat interventions including additional drain placement, upsize/reposition

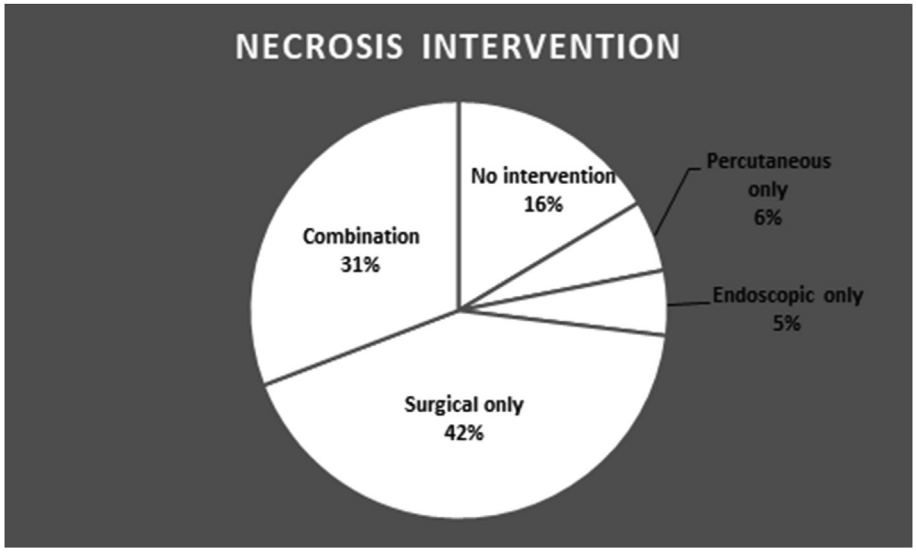

Fig. 2. Necrosis intervention in overall cohort of 714 necrotizing pancreatitis patients treated between 2005 and 2018.

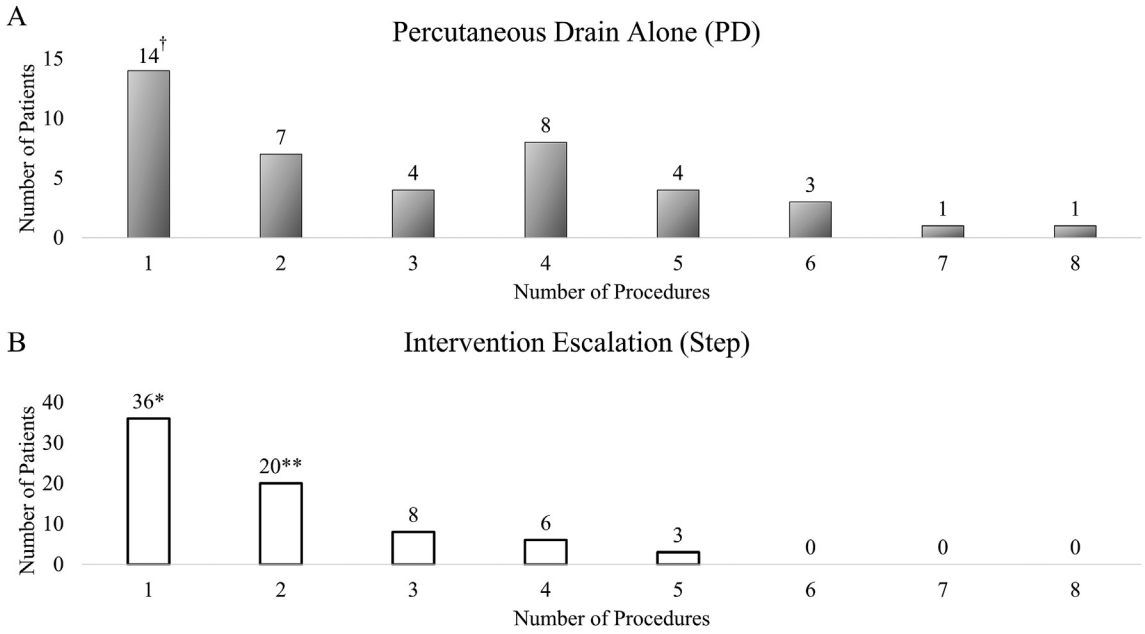

Fig. 3. Number of percutaneous procedures before disease resolution in PD group (A) and number of percutaneous procedures before escalation of intervention in Step group (B). †Three patients died after one percutaneous procedure (PD). *Six patients died after one percutaneous procedure (Step). **Four patients died after two percutaneous procedures (Step).
Abbreviations: PD – percutaneous drain only; Step – patients requiring a step-up in management.

procedures, and drain replacements compared to those patients requiring escalation to more invasive treatment (Step).

No difference was seen in the mean disease duration between the two groups. The mean disease duration was 5.7 months (SD, 3.3) in the PD group and 5.8 months (SD, 4.2) in the Step group, $P = 0.9$. Median follow-up of the overall cohort was 17.9 months (range, 3–150). The mortality of all NP patients undergoing PD as the first step in intervention was 11% (n = 13). No difference was seen in mortality between groups (PD, 7%; Step, 14%; P = 0.3).

Discussion

Management of necrotizing pancreatitis patients who require intervention remains a complex problem for the clinician. Over the last decade, open pancreatic debridement has largely been supplanted by minimally invasive techniques for initial management of pancreatic necrosis. The result of this so called “step-up” approach has been improved patient outcomes; in fact, in one-third of patients percutaneous drainage will obviate the need for further intervention [9,11,12]. This large-volume, single-institution study evaluated 115 patients undergoing PD as the initial step in NP intervention. A comparison of those patients resolving with PD alone and those requiring a "step-up" to further intervention demonstrated that no pattern of necrosis predicted successful management with PD alone. Patients successfully treated with PD underwent more aggressive percutaneous necrosis evacuation including overall percutaneous procedures, additional percutaneous drains, and drain repositioning and/or upsizing. The presence of DPDS significantly decreased the likelihood that PD alone would definitively resolve pancreatic necrosis.

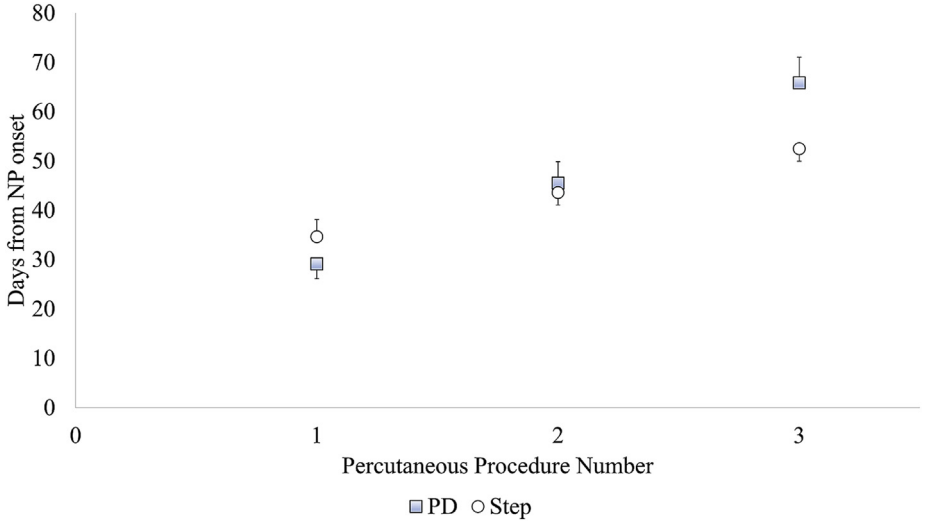

Fig. 4. Comparison of the mean number of days from NP onset to the first (1), second (2), and third (3) percutaneous procedures in the PD and Step groups (*P* range, 0.2–0.8). Error bars represent standard error of the mean.
Abbreviations: NP – necrotizing pancreatitis; PD – percutaneous drain only; Step – patients requiring a step-up in management.

Table 1
Comparison of necrosis morphology between groups.
Abbreviations: PD – percutaneous drain only; Step – patients requiring a step-up in management; SD – standard deviation.

	PD (n = 42)	Step (n = 73)	*P*
Necrosis Field			
Gland Head/Neck, n (%)	24 (57)	38 (52)	0.6
Gland Body/Tail, n (%)	23 (55)	39 (53)	0.9
Lesser Sac, n (%)	42 (100)	73 (100)	1.0
Right Paracolic Gutter, n (%)	9 (21)	19 (26)	0.6
Left Paracolic Gutter, n (%)	15 (36)	27 (37)	0.9
Small Bowel Mesentery, n (%)	17 (40)	26 (36)	0.6
Multi-Field Necrosis, n (%)	30 (64)	48 (56)	0.6
Number of Fields, mean (+/-SD)	3.1 (±1.3)	3.0 (±1.2)	0.8
1-2 fields, n (%)	12 (29)	26 (36)	
3-4 fields, n (%)	26 (62)	39 (53)	
5-6 fields, n (%)	4 (10)	8 (11)	0.7

Distribution of pancreatic necrosis varies between individuals; however, patterns exist and typically include a combination of necrosis in the following anatomic fields: pancreatic head/neck, pancreatic body/tail, lesser sac, left paracolic gutter, right paracolic gutter, and necrosis tracking down the root of the small bowel mesentery. Anatomically each location can provide unique challenges to, or potentially facilitate, interventional approaches. For example, necrosis confined to the lesser sac is amenable to transgastric therapy [20,21]. Intuitively, certain morphology patterns might suggest a higher likelihood of successful management with PD alone. Necrosis involving only peripancreatic soft tissue (i.e. isolated peripancreatic necrosis) is felt by many to portend a better prognosis than pancreatic parenchyma necrosis [22–24]. In the current study, no pattern of necrosis when considered alone or in combination was predictive of successful resolution of pancreatic necrosis with PD alone; in fact, morphology was remarkably similar between groups.

Similar to the heterogeneity in necrosis patterns, heterogeneity in necrosis consistency exists. Further, the consistency of necrosis evolves throughout the disease course; logically, liquid necrosis will drain more easily than solid necrosis. This concept has stimulated efforts to facilitate drainage by promoting the liquefaction of solid necrosis [25,26]. The concept of evolving necrosis character might suggest that drain size (initial, maximum, or final) or the timing of initial drain placement would factor into successful PD therapy. The current series found no difference in the timing of initial drain placement, initial drain size, maximum drain size, or final drain size between groups. Not surprisingly, patients resolving with PD alone underwent significantly more percutaneous procedures than those requiring "step-up", highlighting an important aspect in the care of NP patients. When utilizing PD as a therapy in NP, vigilance in the form of frequent drain repositioning, drain upsizing, or additional drain placement is required to maximize the chance of success. This study further validates a “proactive” approach to PD management following drain placement, as previously reported by the Dutch Pancreatitis Study Group [27]. The use of dual-modality drainage (DMD) combining percutaneous drainage with simultaneous endoscopic transluminal drainage has been promoted by the Virginia Mason group, and recently been adopted by our own group. This approach may decrease escalation to more invasive intervention in select NP patients [28–31]. This technique should be performed by physicians highly experienced with endoscopic intervention on pancreatic necrosis.

The decision to “step-up” is an intricate one; the insult of more invasive intervention must be weighed against the likelihood of success with ongoing attempts at PD. The current study further supports the published literature describing PD success in about one-third of patients with NP requiring intervention [11,12]. The remaining patients pose a clinical dilemma, as no standard exists in determining the timing of “step-up” in care. In the current study, the time to escalation with more invasive treatment was 29 days after initial drain placement. The pancreatologist must be mindful and balance ongoing attempts at minimally invasive management with the ongoing physiologic atrophy in the setting incomplete source control. Objective scientific metrics are needed to help guide complex clinical decision-making.

No statistical difference in mortality was observed between groups; however, the mortality rate in patients requiring an escalation to more invasive intervention (14%) was two-fold higher than

Table 2
Comparison of timing and size of drain placement between groups.
Abbreviations: PD – percutaneous drain only; Step – patients requiring a step-up in management; Fr – French; SD – standard deviation.

	PD (n = 42)	Step (n = 73)	*P*
Days to first drain placement, mean (SD)	29.2 (±19.6)	34.7 (±29.7)	0.3
Initial drain size (Fr), median (range)	14 (10-24)	14 (8-26)	0.8
Maximum drain size (Fr), median (range)	16 (10-32)	14 (8-26)	0.3
Final drain size (Fr), median (range)	16 (10-26)	14 (8-26)	0.6
Days to step-up, mean (SD)	–	29.4 (±24.6)	–
Number of percutaneous interventions prior to step-up, mean (SD)	–	2.0 (±1.4)	–

Table 3
Comparison of the frequency and number of repeat percutaneous intervention between groups including any repeat percutaneous intervention, additional drain placement, drain upsize/reposition, and replacement of dislodged drain.
Abbreviations: PD – percutaneous drain only; Step – patients requiring a step-up in management; SD – standard deviation.

	PD (n = 42)	Step (n = 73)	*P*
Any repeat percutaneous intervention, n (%)	30 (71)	39 (53)	0.1
Number of repeat interventions, mean (+/– SD)	3.2 (±2.5)	2.0 (±1.3)	0.0006
Additional drain, n (%)	21 (50%)	26 (36%)	0.1
Number of additional drains, mean (+/– SD)	1.9 (±1.3)	1.3 (±0.7)	0.01
Drain upsize/reposition, n (%)	25 (60)	28 (38%)	0.03
Number of upsize/reposition, mean (+/– SD)	2.0 (±1.4)	1.5 (±0.9)	0.006
Displaced Requiring Replacement, n (%)	7 (17)	3 (4)	0.02
Number of replaced drains, mean (+/– SD)	1.3 (±0.5)	1.0 (±0.2)	0.01
Number of CT scans, mean (+/– SD)	7.9 (±4.8)	7.0 (±4.8)	0.3

patients resolving with PD alone (7%). This is not a surprising finding, as patients with more severe NP are more likely to require an escalation in therapy [32,33]. A power analysis was performed to determine the sample size required to detect this two-fold increase in mortality. Proceeding under the assumption that one-third of NP patients undergoing PD will resolve without more invasive intervention and mortality rates within each group remain the same as this study, a sample size of 699 patients would be required to detect a statistically significant difference in mortality ($\alpha = 0.05$; $\beta = 0.2$).

Recent work has suggested that patients with multiple organ failure, increasing percent necrosis, heterogeneity on CT scan, and increasing density on CT scan are more likely to fail PD therapy and require an escalation in management [32,33]. The current study identifies DPDS as an additional variable increasing the likelihood of failed PD therapy. Disconnected pancreatic duct syndrome was first described by Kozarek in 1996 [16]. In 1998, Freeny et al. reported the first study utilizing percutaneous drainage as a therapeutic approach in NP. These authors noted over 20 years ago that the presence of DPDS was associated with failure of PD [34]. Walled off necrosis isolated to the lesser sac occurs in 15–20% of NP patients and is amenable to transgastric drainage [20,18]; however, disconnected pancreatic duct syndrome may result in a wide variety of clinical presentations, including isolated lesser sac necrosis or complex, multifield necrosis [35]. Of great interest in the current study was the fact that among those patients with DPDS, about one-third of patients were *successfully* treated with PD alone. The small sample size of this subgroup precludes accurate statistical analysis; however, further study of this fascinating observation is certainly warranted in a larger sample size. Therefore, it should be noted that while those patients with DPDS have a lesser likelihood of achieving definitive disease resolution with PD alone, the simple presence of DPDS should not preclude PD as initial treatment. In the conventional algorithm of NP requiring intervention, control of sepsis can be achieved with percutaneous drainage, allowing for a more measured approach to intervention.

This study is limited by its retrospective nature. Additionally, it does not account for confounding factors influencing the indication for intervention such as severity of acute illness or degree of organ failure. The decision to continue attempts at percutaneous drainage or to escalate therapy is at the discretion of the treating team; more objective empiric metrics are needed to guide this complex therapeutic decision-making. Composition of necrosis (i.e. percent solid) is important, but very challenging to accurately document, particularly in a retrospective analysis. Finally, obtaining the power needed to draw conclusions regarding NP patients remains difficult; however, a strength of this study is the large-volume cohort of NP patients.

Necrotizing pancreatitis is a complex and heterogeneous disease in which treatment methods have undergone a drastic change over the last decade. Percutaneous drain placement is effective as definitive therapy in one-third of patients; however, success cannot be predicted based on patterns of necrosis morphology alone. Patients with disconnected pancreatic duct syndrome are less likely to have percutaneous drain provide definitive management of NP. However, the presence of disconnected pancreatic duct syndrome should not preclude percutaneous drain placement as the first step in the treatment algorithm.

Author contribution

Acquisition, analysis, interpretation of data: TKM, SM, AMR, MGH, AN, EPC, CMS, NJZ.

Conception, drafting, and revision of work: TKM, SM, AMR, MGH, AN, EPC, CMS, NJZ.

Final approval of work: TKM, SM, AMR, MGH, AN, EPC, CMS, NJZ.

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