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ORIGINAL ARTICLE

Percutaneous Endoscopic Step-Up Therapy Is an Effective Minimally Invasive Approach for Infected Necrotizing Pancreatitis

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Abstract

Background Infected pancreatic necrosis (IPN) is a major complication of acute pancreatitis (AP), which may require necrosectomy. Minimally invasive surgical step-up therapy is preferred for IPN.

Aim To assess the effectiveness of percutaneous endoscopic step-up therapy in patients with IPN and identify predictors of its success.

Methods Consecutive patients with AP hospitalized to our tertiary care academic center were studied prospectively. Patients with IPN formed the study group. The treatment protocol for IPN was percutaneous endoscopic step-up approach starting with antibiotics and percutaneous catheter drainage, and if required necrosectomy. Percutaneous endoscopic necrosectomy (PEN) was performed using a flexible endoscope through the percutaneous tract under conscious sedation. Control of sepsis with resolution of collection(s) was the primary outcome measure.

Results A total of 415 patients with AP were included. Of them, 272 patients had necrotizing pancreatitis and 177 (65%) developed IPN. Of these 177 patients, 27 were treated conservatively with antibiotics alone, 56 underwent percutaneous drainage alone, 53 required underwent PEN as a step-up therapy, 1 per-oral endoscopic necrosectomy, and 52 required surgery. Of the 53 patients in the PEN group, 42 (79.2%) were treated successfully—34 after PEN alone and 8 after additional surgery. Eleven of 53 patients died due to organ failure—7 after PEN and 4 after surgery. Independent predictors of mortality were > 50% necrosis and early organ failure.

Conclusion Percutaneous endoscopic step-up therapy is an effective strategy for IPN. Organ failure and extensive pancreatic necrosis predicted a suboptimal outcome in patients with infected necrotizing pancreatitis.

Keywords Acute pancreatitis · Infected pancreatic necrosis · Percutaneous endoscopic necrosectomy · Walled-off necrosis

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Introduction

Acute pancreatitis (AP) is associated with significant morbidity and mortality, and its incidence has been increasing [1, 2]. Acute necrotizing pancreatitis is a severe form of the disease with a mortality of 20–40% [3, 4]. Superadded infection of the necrotic tissue and associated fluid collection(s) is a major complication of AP [5]. Two most important determinants of survival in AP are persistent organ failure and infected pancreatic necrosis (IPN) [6–8]. We and others have shown the extent and infection of the pancreatic necrosis correlated with organ failure and mortality in AP [5, 9].

Most patients with sterile necrosis should be managed conservatively as recommended by various guidelines [10, 11]. For infected necrosis, a step-up treatment strategy is recommended that includes antibiotics, percutaneous catheter drainage, and surgical necrosectomy [12, 13]. A conservative strategy might be successful in up to two-thirds of patients as shown in a meta-analysis [14]. The remaining patients require necrosectomy to control sepsis. Open surgical necrosectomy is associated with significant collateral damage, morbidity, and mortality [13, 15]. Minimal invasive techniques such as video-assisted retroperitoneal debridement (VARD) are preferred due to lower complications [16, 17]. VARD requires a surgical incision along the PCD catheter. Recent studies have shown per-oral endoscopic step-up therapy to be as effective as surgical therapy [18, 19]. Since most patients with IPN undergo percutaneous catheter drainage, the percutaneous tract offers an attractive route for accessing the collection(s) for necrosectomy. Using such an approach, we have shown that percutaneous endoscopic necrosectomy (PEN) under conscious sedation is a feasible, effective, and safe minimally invasive technique in a proof-of-concept pilot study [20]. The objective of the present study was to assess the effectiveness of percutaneous endoscopic step-up therapy in an unselected cohort of patients with IPN and identify predictors of successful outcome.

Methods

This is an observational cohort study carried out in a tertiary care academic center.

Patients All consecutive patients with acute necrotizing pancreatitis who were hospitalized to our center between August 2013 and July 2016 were studied. Informed consent was obtained from all individual participants included in the study. The diagnosis of AP was made in the presence of two of the following features: suggestive clinical features, raised serum amylase (> 3 times the upper limit of normal), and evidence of AP on imaging studies.

Characterization of Acute Pancreatitis

AP was categorized as either interstitial or necrotizing. The severity of AP and the type of fluid collections were diagnosed according to the revised Atlanta classification [21]. Infected pancreatic necrosis (IPN) was suspected if there was evidence of sepsis in the form of persistent fever of > 38 °C beyond the first week of illness, leukocytosis, and worsening clinical course. The diagnosis of IPN was confirmed if pancreatic necrotic tissue/fluid showed the presence of bacteria on culture and/or if there was extra-intestinal gas in the pancreatic bed on a computerized tomography (CT) scan of the abdomen.

Management of Acute Pancreatitis

All patients were managed according to a predefined management protocol as described previously [12]. Standard investigations including complete blood count, serum biochemistry, and imaging were done. A contrast-enhanced computerized tomography (CECT) scan was the main imaging modality which was done as indicated clinically, e.g., planning intervention for infected collections. Supportive management included maintenance of fluid and electrolyte balance, organ support, enteral nutrition, and if indicated antimicrobials. All patients with organ failure were managed in an ICU.

Management of Infected Pancreatic Necrosis

The management protocol was primarily conservative treatment, i.e., all patients with IPN were treated initially with an aggressive medical management in an ICU that included combination antibiotics, organ support, and nutritional therapy. The step-up approach consisted of percutaneous catheter drainage (PCD) of infected collections if there was continuing sepsis despite antibiotics. For PCD, single or multiple 12-F pigtail catheters were placed under CT guidance and gradually upsized to 16–20 F. If no improvement was noted, the treatment was stepped up to percutaneous endoscopic necrosectomy (PEN). Surgical necrosectomy was resorted to if it was deemed most appropriate, i.e., the presence of predominantly solid necrotic debris in the collection, inaccessible location for PCD, or unsuccessful PEN.

Technique of Percutaneous Endoscopic Necrosectomy (PEN)

PEN was done under conscious sedation and analgesia using a combination of midazolam, propofol, and fentanyl. An ultrathin flexible upper gastrointestinal (UGI) endoscope with an outer diameter of 4.9 or 5.5 mm (GIF N180 or GIF

190 N, Olympus, India) was introduced through the percutaneous tract into the collection. The cavity was visualized with CO_2 insufflation. The liquid component was sucked out, and the cavity was lavaged thoroughly with sterile normal saline. Thereafter, a 20–24-F tube was inserted into the cavity. After 2–3 days, the tract was dilated to 12 mm using a balloon dilator (CRE, Boston Scientific, USA). Then, necrosectomy was performed with a standard UGI endoscope (diameter 8.8–9.2 mm), using either a snare and/or a Roth net basket (Video). The cavity was lavaged, and a 28–30-French catheter was placed over the ultrathin endoscope by Seldinger technique. The procedure was repeated every 2–4 days till sepsis was controlled and the cavity was cleared off the necrotic debris (Fig. 1a, b). Thereafter, the large bore tube was replaced with an 18-F tube draining into a colostomy bag. The tube was kept till the fluid output decreased to < 20 ml/day.

Main Outcome Measures

Success as defined by control of the sepsis and resolution of the infected collections was the primary outcome measure. The secondary outcome measure was predictors of the outcome of patients treated with percutaneous endoscopic step-up approach and complications.

Statistical Analysis

Data are presented as mean (SD) or median (range) as appropriate. Student's *t* test and Chi-squared test were applied for comparing quantitative and categorical data, respectively. Univariate and multivariable regression analyses were performed to identify the predictors of success of treatment with age, extent of necrosis, organ failure at admission, acute necrotic collection versus walled-off necrosis (WON) as independent variables. A p value of < 0.05 was taken as significant.

Results

A total of 415 patients with AP were hospitalized from August 2013 to July 2016. The mean age of the patients was 40 ± 14.8 years, and 269 (64.8%) were males. The median interval between the onset of AP and admission to our hospital was 9 days (range 0–345 days). The etiology of AP was gallstone in 208 (50.1%) patients, alcohol in 111 (26.7%) patients, post-ERCP in 24 (5.8%) patients, idiopathic in 57 (13.7%) patients, drugs in 9, metabolic in 4, and biliary ascariasis and trauma in 1 patient each. Of the 415 patients, 330 underwent a CECT scan of the abdomen and 272 were detected to have necrotizing pancreatitis. Of the 415 patients, 75 had mild AP, 123 had moderately severe AP, and 217 patients had severe AP. Among the 217 patients with severe AP, multi-organ failure was present in 113 patients while 104 patients had single organ failure; 170 of them had developed early-onset organ failure. One hundred and seventy-seven patients developed infected necrosis. The relevant clinical data of the patients are provided in Table 1.

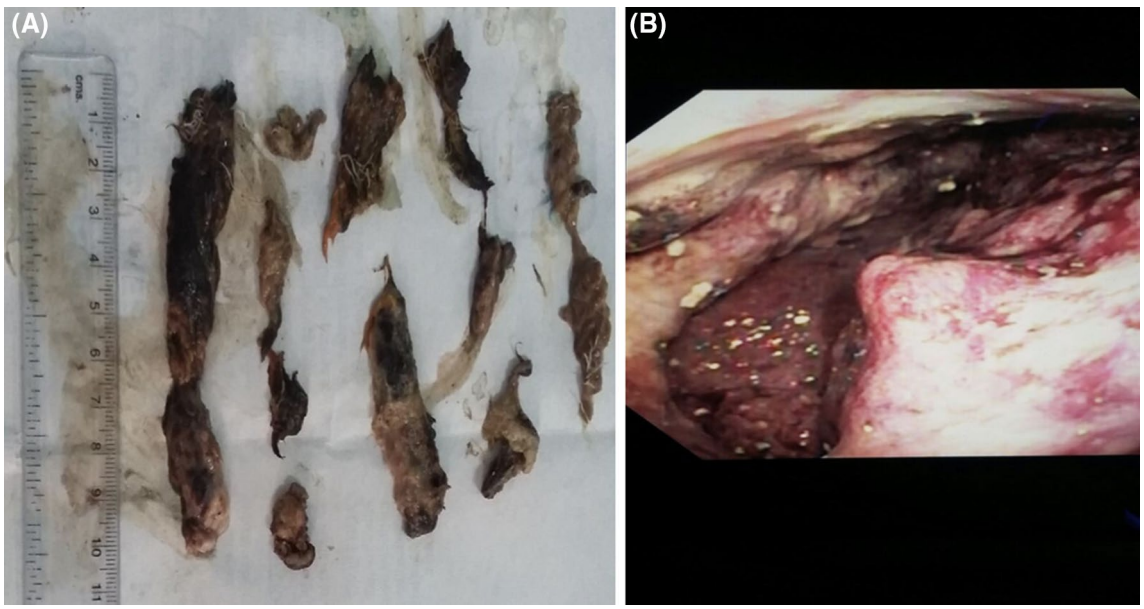

Fig. 1 **a** Necrotic tissue removed during a session of percutaneous endoscopic necrosectomy; **b** the inside view of a cavity after complete clearance of infected necrotic material and lavage

Table 1 Clinical characteristics of patients with acute pancreatitis

Parameters	Value
Number of patients	415
Age (mean ± SD) (years)	40 ± 14.8
Sex (male/female)	269/146
Median (range) interval between onset and admission (days)	9 (0–345)
Etiology	
Gall stone *n* (%)	208 (51)
Alcohol *n* (%)	111 (27)
Others *n* (%)	96 (22)
Severity of acute pancreatitis (*n*)	
Mild	75 (18.1%)
Moderately severe	123 (29.6%)
Severe	217 (52.3%)
Organ failure *n* (%)	217 (52.3)
Single organ failure (*n*)	104
Multi-organ failure (*n*)	113
Necrotizing pancreatitis (*n*)	272
Infected pancreatic necrosis (*n*)	177/272 (65%)
Mortality (*n*)	125/415 (30%)

n Number of patients

Management and Outcome of Patients with Necrosis and Acute Fluid Collections (Fig. 2)

Of the 272 patients with necrotizing pancreatitis, 33 patients had no collection, 142 had acute necrotic collections (ANC), and 97 had walled-off necrosis (WON).Of the 142 patients with ANC, 102 developed infected ANC. Following the percutaneous endoscopic step-up therapy protocol, 20 were treated conservatively with antibiotics alone and 82 patients underwent PCD, 26 patients required percutaneous endoscopic necrosectomy, and 27 patients required surgical necrosectomy—19 following PCD and 8 after PEN because of failure to control sepsis. Forty-five (44%) out of 102 patients with infected acute necrotic collections died, all due to persistent organ failure—34 had early-onset persistent organ failure and 11 had late-onset sepsis-related organ failure.

Management and Outcome of Patients with WON

Of the 97 patients with WON, 22 were sterile. Of these 22 patients, 20 recovered and 1 died due to persistent organ failure and 1 due to massive bleeding. Of the 20 patients who recovered, 13 were managed conservatively, 4 underwent PCD, 2 underwent per-oral direct endoscopic drainage and necrosectomy (DEN), and one patient underwent laparoscopic cystogastrostomy.

Of the 75 patients with infected WON, 6 underwent direct surgery because of large amount (> 50%) of solid necrotic debris. In remaining 69 patients, 7 recovered with antibiotics alone, 19 patients were managed with PCD alone, 27 patients underwent PEN following PCD, and 1 patient underwent per-oral endoscopic necrosectomy. Nineteen patients required surgery—15 following PCD and 4 after PEN. Twenty-one (28%) of the 75 patients with infected WON died due to persistent organ failure and continued sepsis.

Adverse Events of Percutaneous Endoscopic Necrosectomy

The demographic data and details of PEN procedure are provided in Table 2. Of the 53 patients who underwent PEN, 7 patients had adverse events following PEN—aspiration pneumonia in 2, peritonitis in 2, and paralytic ileus and subcutaneous emphysema and self-limiting bleeding in one patient each. Except peritonitis, other complications were managed conservatively and all the 7 patients improved. Eleven of 53 patients died due to organ failure—7 after PEN and 4 after additional surgery. Eight of the 11 patients died at the stage of infected acute necrotic collections.

Among patients who underwent PEN, the catheter drain was removed after a median of 48 days (range 14–90) from the time of PCD insertion. Four (7%) patients developed pancreaticocutaneous fistula after PEN procedure, all of them resolved with conservative management but none developed enteral fistula. Pseudoaneurysm-related bleeding was seen in 7 patients (4%), and splanchnic venous thrombosis was seen in 4 (2.3%) patients. Massive bleeding due to pseudoaneurysm contributed to mortality in 3 patients with infected necrosis. There was no symptomatic recurrence till 12 months after AP.

Predictors of Outcome Following Percutaneous Endoscopic Step-Up Approach for IPN

Of the 171 patients with IPN treated with the percutaneous endoscopic step-up approach, 105 (62%) survived with a mortality of 38%. The differences between the survivors and non-survivors are provided in Table 3. The independent predictors of failure of the step-up approach in multivariable analysis were early persistent organ failure [OR (95% CI) 4.2 (2–8.8); $p = 0.001$] and extensive pancreatic necrosis > 50% [OR (95% CI) 2.6 (1.2–5.5); $p = 0.01$] (Table 4).

Discussion

Infected pancreatic necrosis is a dreaded complication and an important determinant of survival in patients with AP. There are limited data from randomized controlled trials

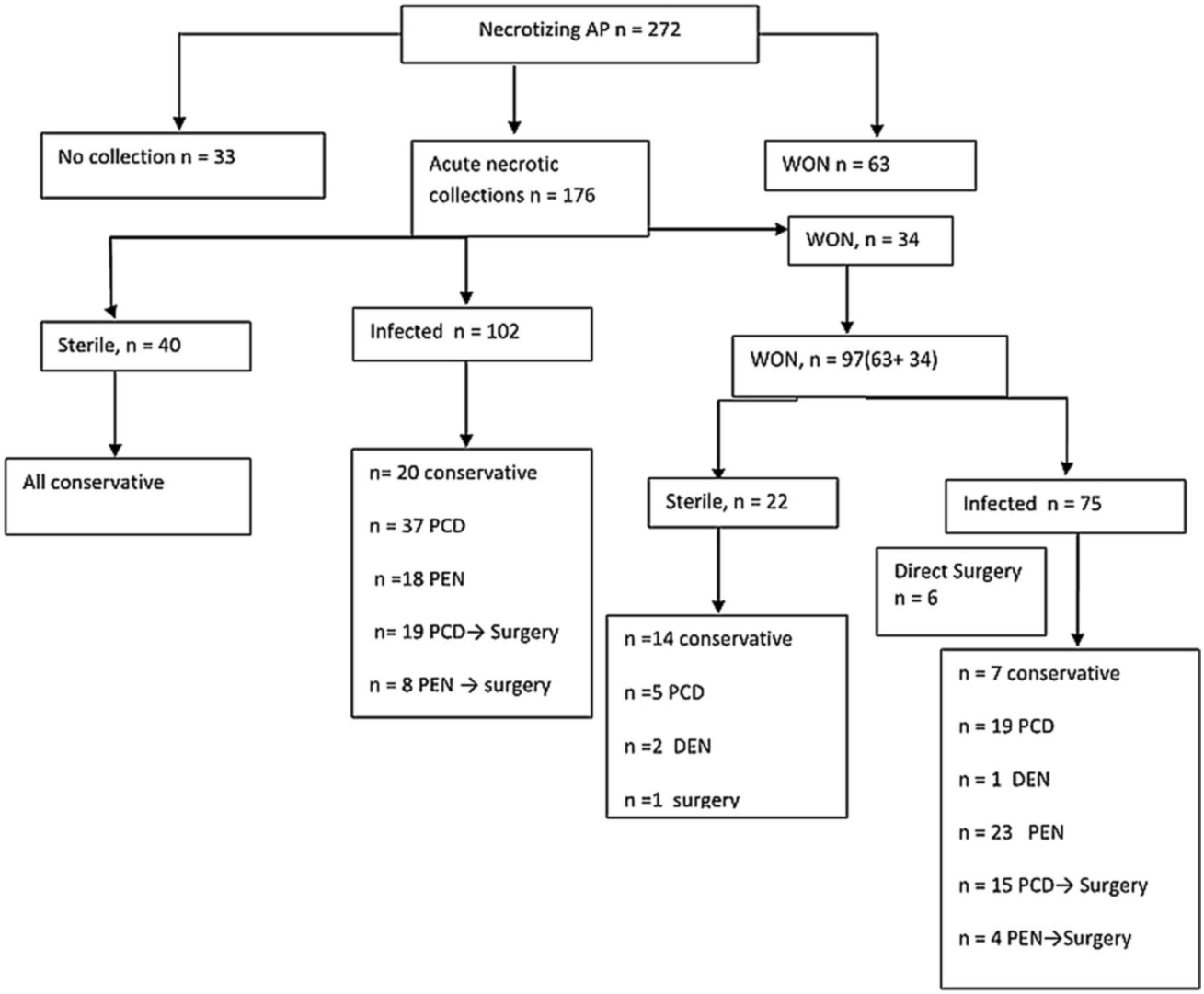

Fig. 2 Management and outcome of patients with necrotizing pancreatitis. Numbers represent the number of patients who received a particular type of treatment. *AP* Acute pancreatitis, *WON* walled-off necrosis, *PCD* percutaneous drainage, *PEN* percutaneous endoscopic necrosectomy, *DEN* direct per-oral endoscopic necrosectomy

for the optimal management of patients with necrotizing pancreatitis. A step-up approach starting with antibiotics, percutaneous drainage, and finally surgical necrosectomy is currently considered the standard of care for managing patients with IPN although the quality of evidence is low to very low according to a recent Cochrane review [22, 23]. Percutaneous drainage is generally accepted as the first intervention in patients with infected collections. It helps control sepsis, stabilizes the patient before further intervention can be undertaken, and may prove to be curative in a subset of patients [13, 14]. Percutaneous tract was first exploited for nephroscopic interventions and later for VARD [24]. We have used the same tract for percutaneous endoscopic necrosectomy (PEN) and shown its feasibility, safety, and efficacy in treating IPN in a pilot study [20]. In the present study, we studied the effectiveness of percutaneous endoscopic step-up therapy in a large cohort of patients and assessed the predictors of its success.

We observed that the percutaneous endoscopic step-up approach was effective in 62% of patients with IPN with a mortality of 38%. Among the predictors of success of percutaneous endoscopic step-up therapy, persistent organ failure was the most important predictor for unsuccessful PEN in the present study. A combination of infected necrosis and organ failure termed "critical pancreatitis" as per the determinant-based classification has the highest mortality [25]. A recent large multicenter Dutch study has shown a mortality of 44% in patients with persistent organ failure and 29% mortality in those with infected necrosis [26].

Table 2 Demographic details of patients with infected necrosis treated with PEN

Parameters	Value
Number of patients	53
Age (mean ± SD) (years)	39 ± 13
Sex (male/female)	34/19
Etiology	
Gall stone *n* (%)	31 (58)
Alcohol *n* (%)	10 (19)
Others *n* (%)	12 (23)
Acute necrotic collections (*n*)	26
Walled of necrosis (*n*)	27
Median number of sessions of PEN (range)	4 (2–15)
Median interval from the diagnosis to PCD (days)	23 (8–187)
Median time period between PCD and PEN (days)	17 (4–75)
Median interval from the onset of AP to PEN (days)	45 (26–196)
Median duration of hospital stay (days)	52 (13–120)
Survival (%)	42/53 (79)

n Number of patients, *PCD* percutaneous catheter drainage, *PEN* percutaneous endoscopic necrosectomy

Another predictor of failure was extensive necrosis. Percutaneous endoscopic step-up therapy had a worse outcome in patients with infected acute necrotic collections compared to those with WON in the present study. Although necrosectomy is easier in patients with WON, some patients with IPN do require early necrosectomy due to worsening sepsis even after PCD but the outcome is inferior [27].

Among minimally invasive necrosectomy techniques, VARD is an effective technique [28]. We also subject some of our patients to direct VARD or as a rescue procedure. Per-oral direct endoscopic necrosectomy (DEN) has also been shown to be effective in patients with infected necrosis. Two case series had shown its efficacy but with significant complications [29, 30]. Two recent randomized trials have shown that per-oral endoscopic step-up therapy is similar to surgical step-up therapy [18, 19]. However, most patients undergo percutaneous catheter drainage as the preferred first intervention more so in patients with acute infected necrotic collections. The percutaneous route offers an easy approach to perform further intervention. The choice of the procedure depends both on location of collection and local expertise. Collections with deep retroperitoneal and/or pelvic extension are more suitable for the percutaneous drainage followed by percutaneous endoscopic step-up approach. However, collections closely adherent to the stomach and/or duodenum are amenable for drainage by per-oral endoscopic cystogastrostomy or cystoduodenostomy to mitigate some of the long-term complications such as disconnected pancreatic duct syndrome. The preferred timing of per-oral endoscopic drainage is after 4 weeks at the stage of WON. However, a recent study by Trikudanathan et al. [31] has shown that endoscopic drainage and necrosectomy can be done with good outcome even before 4 weeks in selected

Table 4 Univariate and multivariable analyses for predictors of unsuccessful step-up approach for infected necrosis

Variable	Univariate		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Necrosis > 50%	2.7 (1.4–5.5)	0.004	2.6 (1.2–5.5)	0.01
Early organ failure	5 (2.6–9.7)	0.001	4.2 (2–8.8)	0.001
ANC	1.8 (0.95–3.4)	0.07		ns

ANC Acute necrotic collection, *ns* not significant

Table 3 Comparison of survivors and non-survivors in patients with infected necrosis

Parameters	Total *n* = 171	Survivors *n* = 105	Non-survivors *n* = 66	*p* value
Age (mean ± SD) (years)	38 ± 14	38 ± 13	39 ± 15	0.4
Male *n* (%)	118 (69)	77 (73)	41 (62)	0.12
Etiology				0.8
Gall stone *n* (%)	91 (53)	54 (51)	37 (56)	
Alcohol *n* (%)	47 (28)	28 (27)	19 (29)	
Others *n* (%)	33 (19)	23 (22)	10 (15)	
Acute necrotic collection *n* (%)	102 (59)	57 (54)	45 (68)	0.07
CTSI	9 (2–10)	8 (2–10)	10 (2–10)	0.07
APACHE II at admission	8 (0–28)	6 (0–16)	13 (3–28)	0.001
Marshall score at admission	2 (0–8)	0 (0–4)	3 (0–8)	0.001
Necrosis > 50% *n* (%)	109 (64)	58 (55)	51 (77)	0.004
Early organ failure *n* (%)	74 (43)	30 (29)	44 (66)	0.001
Median duration of hospital stay (days)	30 (1–120)	30 (7–120)	30 (1–100)	0.2

CTSI Computed tomography severity index, *APACHE* Acute Physiology and Chronic Health Evaluation score

patients with ongoing sepsis and organ failure. These emerging data are likely to shift the trend toward more per-oral endoscopic drainage even in acute infected collections in suitable patients.

Patients with infected necrosis are sicker, and performing repeated per-oral endoscopic procedures is a difficult proposition particularly in those with respiratory failure. The risks of general anesthesia and the probability of delay in extubation are high in such patients. The acceptability of PEN in our experience is much better than DEN. The advantages of PEN include: (1) It can be done in areas inaccessible for per-oral endoscopic necrosectomy particularly laterally placed collections in paracolic areas and pelvis, (2) a flexible endoscope allows more effective necrosectomy with the ability to maneuver the scope into different extensions of the cavity for the removal of debris unlike a rigid nephroscope or laparoscope, (3) it can be done at patient's bedside, (4) it avoids the need for general anesthesia, (5) the procedure time can be tailored to a patient's general condition with the option of repeat sessions later, and (6) lavage alone helps control sepsis and stabilizes a patient's condition before a definitive surgical procedure could be undertaken.

A few other reports have shown that PEN is a useful minimally invasive technique for necrosectomy but in smaller number of patients [32–34]. Tang et al. [35] in a series of 42 patients used a choledochoscope through a 22 F tract for guided necrosectomy and showed a high success rate of 90%. Their patients required a mean of 8.5 sessions at a mean interval of 4.5 days. However, the narrow working channel of a choledochoscope is a limitation for necrosectomy. Esophageal self-expendable metal stent (SEMS) placement for PEN has been reported in small case series [36, 37]. One advantage of this approach is that sequential upgradation of PCD catheters to 30–32 F prior to PEN is not required. Potential disadvantages, however, could be higher rates of pancreaticocutaneous fistula due to larger diameter of the tract and risk of bleeding due to metal stent within the cavity after it has collapsed. How long to keep the metal stents in situ is another issue that needs to be addressed. Prospective studies with a larger sample size are needed to validate the use of percutaneous metal stent.

PEN should be regarded as a surgical procedure albeit minimally invasive. Thus, caution should be exercised when performing PEN. Blood vessels are often running within the collection and must be carefully avoided during the procedure. Adherent necrotic tissue is difficult to take out and should not be forcibly removed. PEN should be performed through retroperitoneal route and not transperitoneal route because of high risk of peritonitis.

We did have complications in a few patients. Two patients developed peritonitis and required surgery. It was most likely due to spillage of infected fluid under pressure from the collections to the peritoneal cavity. Lavage with H_2O_2 and or povidone-iodine could have contributed to the development of peritonitis. That is why we have stopped doing lavage with these fluids. Four out of 53 (7%) patients developed pancreaticocutaneous fistula after PEN procedure, all of them resolved with conservative management. There were no enteral fistulae in any patients undergoing PEN. Contrary to some other reports particularly after surgical necrosectomy, we found a much lower rate of pancreaticocutaneous fistula. The reasons could be downsizing of the catheter drain to 16–18 F after clearance of the cavity and converting the gravity-assisted drain bag to a colostomy bag. Bleeding due to tract dilatation was not seen in any patient probably because of our technique of graded dilatation of the tract over 2–3 sessions.

There are certain limitations of our study. Its observational nature without a comparative arm may introduce bias in interpretation of results. The mortality was substantial in our patients. However, large series from experienced centers have also shown a mortality of around 40% in patients with organ failure [26]. Another limitation is that we did not evaluate long-term sequelae such as endocrine and exocrine insufficiency in this cohort.

In conclusion, percutaneous endoscopic step-up approach is a safe and effective strategy in patients with IPN. Persistent organ failure and extensive necrosis predict suboptimal outcome. Infected necrosis is a complex disease, which requires team work and individualized approach to patient management [38].

Author's contribution SJ, RP contributed to acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision, and final approval of the manuscript; SB, SKJ, RD, NRD, KSM, SRG, PS contributed to analysis and interpretation of data, drafting of the manuscript, critical revision, and final approval of the manuscript; PKG contributed to study concept and design, analysis and interpretation of data; study supervision, drafting of the manuscript, critical revision, and final approval of the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethical consideration Institutional ethical clearance was obtained for two studies on natural course and outcomes of patients with AP.

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