# Early (<4 Weeks) Versus Standard (≥ 4 Weeks) Endoscopically Centered Step-Up Interventions for Necrotizing Pancreatitis

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OBJECTIVES: **Current guidelines for necrotizing pancreatitis (NP) recommend delay in drainage ± necrosectomy until 4 or more weeks after initial presentation to allow collections to wall off. However, evidence of infection with clinical deterioration despite maximum support may mandate earlier (<4 weeks) intervention. There are concerns, but scant data regarding risk of complications and outcomes with early endoscopic intervention. Our aim was to compare the results of an endoscopic centered step-up approach to NP when initiated before versus 4 or more weeks.**

METHODS: **All patients undergoing intervention for NP were managed using an endoscopically centered step-up approach, with transluminal drainage whenever feasible, ±necrosectomy, and/or percutaneous catheter drainage as needed, with surgery only for failures. Interventions were categorized as early or standard based on timing of intervention (<4 weeks or ≥ 4 weeks from onset of pancreatitis). Demographic data, indications and timing for interventions, number and type of intervention, mortality and morbidity (length of stay in hospital and ICU) and complications were compared.**

RESULTS: **Of 305 patients with collections associated with NP, 193 (63%) (median age-52 years) required intervention, performed by a step-up approach. Of the 193 patients, 76 patients underwent early and 117 patients standard intervention. 144 (75%) interventions included endoscopic drainage ± necrosectomy. As compared with standard intervention, early intervention was more often performed for infection (91% vs. 39%, $p<0.05$), more associated with acute kidney injury (43% vs. 32%, $p=0.09$), respiratory failure (41% vs. 22%, $p=0.005$), and shock (13% vs. 4%, $p<0.05$). Organ failure improved significantly after intervention in both groups. There was a significant difference in mortality (13% vs. 4%, $p=0.02$) and need for rescue open necrosectomy (7% vs. 1%, $p=0.03$) between groups. Patients undergoing early intervention had increased median hospital (37 days vs. 26 days, $p=0.01$) and ICU stay (median 2.5 days vs. 0 days, $p=0.001$). There was no difference in complications.**

CONCLUSIONS: **When using an endoscopically centered step-up strategy in necrotizing pancreatitis, early (<4 weeks) interventions were more often performed for infection and organ failure, with no increase in complications, similar improvement in organ failure, slightly increased need for surgery, and relatively low mortality. Early endoscopic drainage ± necrosectomy should be considered when there is a strong indication for intervention.**

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## INTRODUCTION

Acute pancreatitis (AP) can vary markedly in severity. Although the majority of patients have a mild and uneventful course, ~5–10% develop necrotizing pancreatitis [1]. Mortality ranges from ~15% in patients with sterile necrosis to as much as 39 % in patients with infected necrosis, which occurs in ~40–70 % of cases with necrotizing pancreatitis [1–5]. Infected necrosis is generally regarded as a late event in the natural course of acute pancreatitis. However, in a quarter of patients, infection can occur as early as the first week of the disease [6].

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Current criteria categorize collections occurring 4 weeks or less after presentation as "acute necrotic collections", and those at more than 4 weeks as "walled off necrosis" [1]. Published guidelines for the management of necrotizing pancreatitis recommend delay in invasive interventions where feasible for at least 4 weeks after initial presentation to allow the collection to become "walled-off" [2–4]. It has been suggested that this delay enables easier drainage and debridement and mitigates the risk of complications or death, but these concerns are primarily based on literature involving surgical intervention [7, 8]. However, necrotizing pancreatitis with clear evidence of infection, and clinical deterioration despite maximum medical support, may sometimes warrant earlier (<4 weeks) intervention for drainage and/or debridement. A "step-up" approach involves initial minimally invasive drainage followed by on-demand necrosectomy and is the most accepted and studied approach to intervention for walled-off necrosis [4, 9–12]. Initial drainage is increasingly performed endoscopically [5, 9, 13–15]. However, endoscopic intervention is often deferred to percutaneous or even surgical drainage in the early stages of necrotizing pancreatitis particularly when collections are not in contact with the GI tract or extend into inaccessible regions for endoscopic debridement [2]. Although the use of a step-up approach has become standard of care for walled-off necrosis, the safety and efficacy of an endoscopically centered approach earlier than 4 weeks has not been well studied.

The purpose of this study was to compare the clinical outcomes of a step-up approach to necrotizing pancreatitis when initiated before versus after 4 weeks.

## METHODS

### Patients

Consecutive patients with collections resulting from necrotizing pancreatitis and undergoing any form of drainage/necrosectomy at University of Minnesota Medical Center over a 6-year period from 2010 to 2016 were identified from a prospectively maintained database. Based on timing of intervention, patients were categorized into two groups: "early" or "standard" based on timing of intervention (<4 weeks or ≥ 4 weeks from onset of pancreatitis). Demographic data, indication for and timing of intervention, number and type of intervention, clinical outcomes, and complications (procedure-related adverse events, organ dysfunction, length of stay, ICU stay, and mortality) were compared between the groups.

### Imaging

All available computed tomography (CT) imaging prior to initial intervention were independently reviewed by SM and were categorized using a classification system similar to the one adopted by the Dutch pancreatitis group [16]. Morphological criteria on CT such as size of the collection (maximal length of collection), location of the collection (pancreatic vs. peripancreatic), degree of encapsulation of the collection, contents of the collection, presence of gas bubble within collection, and presence of ascites was compared between both the groups.

### Interventions

All management decisions regarding interventions were made in a multi-disciplinary manner involving pancreatologists/therapeutic endoscopists, interventional radiologists, intensivists, and surgeons using our previously described algorithm [5]. Patients needing interventions were managed using an endoscopically centered "step-up approach" based on endoscopic and/or percutaneous catheter drainage as felt optimal for first line treatment, with subsequent endoscopic necrosectomy as required and with video-assisted retroperitoneal debridement (VARD) or open surgery reserved for treatment failures or severe complications such as peritonitis, ischemic bowel/perforation, or clinical failure of step-up approach. Endoscopic transluminal drainage (ETD) was the preferred initial approach for management of necrotic collections adjacent to the stomach and duodenum. Primary percutaneous drainage was typically reserved for collections not amenable to endoscopic therapy due to a lack of contact with the gastric or duodenal wall. Adjunctive percutaneous drainage was performed in addition to endoscopic drainage in the setting of large necrotic collections with deep retroperitoneal extension, peritoneal involvement, and for scattered multifocal collections. An entirely retroperitoneal approach was strongly preferred in order to allow for subsequent endoscopic debridement via sinus tract endoscopy (STE). Transperitoneal drain placement was reserved for collections not amenable to a retroperitoneal approach due to intervening bowel or a collection location completely within the peritoneal cavity [2, 9, 17–19].

The initial choice for transluminal stent evolved over the course of the study and ranged from multiple plastic double-pigtail stents, to single fully covered metallic biliary or esophageal stents, and eventually to lumen-apposing metal stents (LAMS). Endoscopic transluminal necrosectomy (ETN) was performed as needed after initial drainage, based on clinical and radiographic response, typically within 3 to 5 days after ETD for patients with infected necrosis and organ failure, or later for patients with less acute illness and/or primarily liquified collections. Necrosectomy was repeated as needed based on the clinical course and until there was complete resolution of solid necrosis. Following completion of debridement, all stents were removed unless there was evidence of disconnected pancreatic duct by imaging, in which case 7 or 10 Fr plastic double-pigtail stents were left in cystenterostomy tracts indefinitely. Patients with adjuvant percutaneous drainage catheters in communication with transluminal stents and thus stomach or duodenum were treated with vigorous flushing and lavage (typically 100–150 cc of saline every 6–8 h). In cases with deep, endoscopically inaccessible cavities, and refractory solid necrosis, the percutaneous drains were gradually upsized to 24 F or greater. Sinus tract endoscopy was then performed by the advanced endoscopy service using flexible forward viewing video endoscopes through the retroperitoneal percutaneous drain tracts [20]. Alternatively, a small number of selected cases underwent VARD through this percutaneous catheter tract by the surgical service using both rigid and flexible instruments. Open surgical necrosectomy was reserved for patients with progressive clinical deterioration despite maximal minimally invasive approaches or in cases with evidence of bowel infarction or perforation mandating initial surgical intervention.

### Follow-up

Post-intervention follow-up included scheduled procedural or pancreas clinic visits with interval cross-sectional imaging as needed to evaluate residual necrosis, stent position, and fistulae patency.

### Outcomes

The primary study outcome was mortality and need for rescue open necrosectomy in both groups. Secondary outcome measures included improvement in new-onset multi-organ failure after intervention, length of hospital stay (LOS), length of ICU stay (ICU-LOS), and complications. Organ failure was defined as per the modified Marshall scoring system used in the revised Atlanta classification [1, 21]. Acute respiratory failure was defined as $PaO_2$ of 60 mm of Hg despite fraction of inspired oxygen ($FIO_2$) of 25% or need for mechanical ventilation. Acute kidney injury was defined as serum creatinine level more than 1.9 mg/dL after rehydration, or new need for hemofiltration or hemodialysis. Circulatory failure was defined as systolic blood pressure below 90 mm Hg unresponsive to fluid resuscitation or need for inotropic pressor support [21]. Multi-organ failure was defined as failure of two or more organ systems for 48 h or longer.

### Complications

Complications were defined according to the American Society of Gastrointestinal Endoscopy criteria that include infection, bleeding, perforation, fistulae, and new-onset diabetes [22, 23]. Bleeding was defined as hemorrhage needing blood transfusion or requiring subsequent endoscopic or radiologic intervention for hemostasis. New-onset diabetes was defined as either HbA1C > 7 and/or need for anti-hyperglycemic agents or insulin during follow-up.

### Statistical analysis

Descriptive statistics included continuous data presented as median and interquartile range (IQR), and categorical data were presented as frequencies and proportions. Univariate analysis was performed to check for significance between the two groups by using the two-tailed Student *t*-test or Mann–Whitney *U* test (for continuous variables) and $\chi^2$ test or Fisher exact test (for categorical variables) where appropriate. *p* values ≤ 0.05 were considered significant. Statistical analyses were performed using Statistical Analysis Software 9.3 (SAS Institute, Cary, NC).

## RESULTS

### Baseline characteristics

A total of 305 patients with necrotizing pancreatitis were managed at our center during the study period. 193 (63%) of these patients underwent intervention for drainage and/or debridement of necrotic collections. In total, 171 (89%) of 193 patients were referred from other facilities after failing conservative management or initial intervention. Baseline and clinical characteristics of the 193 patients included in the study are outlined in Table 1 with no significant differences between patients undergoing interventions at less than 4 weeks (early), versus 4 or more weeks after AP (standard). Patients undergoing early interventions tended to be older (median age 55 years vs. 50 years) however this was not statistically significant ($p = 0.14$). The proportion of males and females were comparable between groups. The most common etiology for pancreatitis was biliary (45% in both the groups) followed by alcohol (25% vs. 26%).

### Imaging

The maximum diameter of collections was significantly larger in the early group (175 mm vs. 140 mm, $p < 0.005$) as outlined in Table 2. Both a pancreatic and peripancreatic component with mixed solid and liquid contents were present in the majority of patients. Completely encapsulated collections were present in only in 5 (7%) of the early group as compared to 48 (43%) of the standard group ($p < 0.005$). Ascites was noted to be significantly more common in the early intervention group (68% vs.33%, $p < 0.001$).

### Interventions

New-onset organ failure was more frequent in patients undergoing early interventions, with 43% vs. 32% ($p = 0.09$) developing acute kidney injury and 41% vs. 22% ($p = 0.005$) acute respiratory failure needing mechanical ventilation. Hypotension needing vasopressor support was also more frequent in early intervention group (13% vs 4%), $p = 0.03$. Interventions performed before 4 weeks were primarily (91%) performed for infected necrosis. Infection (39%), persistent unwellness (39%), and gastric outlet

**Table 1 Baseline demographic data of all necrotizing pancreatitis who underwent intervention (<4 weeks) vs. standard (≥4 weeks)**

| | NP < 4 weeks (*n* = 76) | NP ≥ 4 weeks (*n* = 117) | *p* value |
|---|---|---|---|
| Median age (years), IQR | 55 (39–68) | 50 (37–63) | 0.143 |
| *Sex* | | | 0.189 |
| Male | 51 (67.1%) | 89 (76.1%) | |
| Female | 25 (32.9%) | 28 (23.9%) | |
| *Race* | | | |
| White | 66 (86.8%) | 107 (91.5%) | 0.059 |
| African American | 5 (6.6%) | 1 (0.9%) | Reference |
| Other | 4 (6.6%) | 9 (7.7%) | 0.074 |
| *Etiology for pancreatitis* | | | |
| Biliary | 34 (44.7%) | 53 (45.3%) | Reference |
| Alcohol | 19 (25.0%) | 30 (25.6%) | 0.972 |
| Other etiology[a] | 9 (11.8) | 10 (8.5) | 0.813 |
| Idiopathic | 14 (18.4%) | 24 (20.5%) | 0.506 |

*IQR* interquartile range, *NP* necrotizing pancreatitis
[a]Other etiologies (ANC—drug-induced 2, hypertriglyceridemia 4, post ERCP 2, other 1; WON—hypertriglyceridemia 4, post ERCP 1, other 5)

**Table 2 Imaging characteristics of the necrotic collections < 4 weeks vs. ≥ 4 weeks**

| Nature of necrotic collections | NP < 4 weeks, *n* = 76, *n* (%) | NP ≥ 4 weeks, *n* = 117, *n* (%) | *p* value |
|---|---|---|---|
| Median size of collection in mm (IQR) | 175 (134–234) | 140 (92–186) | **0.001** |
| Location of necrosis | | | |
| Pancreatic | 2 (2.7) | 15 (13.3) | Reference |
| Peripancreatic | 16 (21.6) | 16 (14.1) | **0.015** |
| Both | 56 (75.8) | 82 (72.6) | **0.035** |
| *Degree of encapsulation* | | | |
| No wall | 6 (8.1) | 2 (1.8) | 0.08 |
| Some wall formation | 36 (48.6) | 23 (20.3) | **0.021** |
| Extensive wall formation | 27 (36.5) | 40 (35.4) | Reference |
| Complete wall formation | 5 (6.8) | 48 (42.5) | **0.0004** |
| Contents | | | **0.0002** |
| Only solid | 0 | 1 | |
| Only liquid | 4 | 30 | |
| Both solid and liquid | 70 (94.6) | 82 (72.6) | |
| Number of collections | | | 0.335 |
| Single | 53 (72.6) | 89 (78.8) | |
| Multiple | 20 (27.4) | 24 (21.2) | |
| Presence of gas bubbles | 19 (26.0) | 19 (16.8) | 0.128 |
| Presence of ascites | 50 (67.6) | 37 (32.7) | <**0.0001** |

*p* value calculated using $\chi^2$ test or Fisher exact test for categorical variable and Kruskal–Wallis test for continuous variables where appropriate.
*IQR* interquartile range
Bold values represent *p*-values which were significant and hence important

obstruction (13%) were the most common primary indications for interventions performed at 4 or more weeks (as shown in Table 3).

Endoscopic transluminal drainage was the initial intervention in the majority of patients in both the early and standard groups (62% vs. 77%) respectively. Percutaneous catheter drainage was the initial intervention in 29% of patients undergoing early cases versus 14% of patients undergoing standard intervention (as shown in Fig. 1) ($p = 0.47$). Five (7%) patients in the early group and six (5%) patients in the standard group were treated by immediate open necrosectomy due to acute severe decompensation with either peritonitis or abdominal compartment syndrome. Significantly larger number of patients in the standard group (27% vs 9%, $p = 0.002$) were managed only by endoscopic transluminal drainage. Ten (13%) patients in the early group and six (8%) patients in the standard group were managed only by percutaneous drainage. Majority of patients in both early and standard group needed necrosectomy (71% vs 62%, $p = 0.2$).

### Outcomes

Significantly increased mortality (13% vs. 4%, $p = 0.02$) and need for open necrosectomy (7% vs. 1%, $p = 0.04$) occurred in patients undergoing early interventions. In addition, LOS (median (IQR) 37 days (27–61 days) vs. 26 days, (0–207 days), $p < 0.05$) and length of ICU stay (median (IQR) 2.5 days (0–22 days) vs. 0 days (0–3 days), $p < 0.05$) were significantly longer in patients undergoing early interventions, as was need for adjuvant percutaneous drainage (32 (42%) vs. 25 (21%), $p < 0.005$). In early as well as standard intervention groups organ failure improved substantially within 1 week after step-up intervention (as shown in Fig. 2). Among 12 patients on dialysis who underwent early step-up intervention, 7 (58%) became dialysis independent after 1 week. Similarly, 16 (75%) of the 30 patients needing mechanical ventilation were weaned off respiratory support within 1 week following intervention. 7 (70%) of 10 patients needing inotropic pressor support for circulatory failure, came off pressors within 1 week.

### Adverse events

Clinically significant hemorrhage related to either cystenterostomy or pseudoaneurysm was comparable between groups (11% vs. 10%, $p > 0.05$), including bleeding that required blood transfusion and/or subsequent endoscopic or percutaneous intervention. Transluminal stent occlusion and infection needing repeat intervention was frequent in both the groups (40% vs. 33%, $p > 0.05$). There was no difference in the rate of fistulae (cyst-enteric, enterocutaneous, and pancreaticocutaneous) between the two groups (33% vs. 21%, $p > 0.05$). However, perforation occurred only in the patients who underwent intervention beyond 4 weeks ($n = 7$). Four (57%) of these 7 patients with perforation needed exploratory laparotomy, while three were managed conservatively. The incidence of new-onset diabetes was similar in both the two groups (20% vs. 21%, $p > 0.05$).

## DISCUSSION

The revised Atlanta criteria have standardized morphological characterization of collections based on the time elapsed after onset of pancreatitis, the contents of the cavities, and encapsulation of the wall [1, 24]. Accordingly, acute necrotic collections are generally thought to occur within the first 4 weeks and walled-off necrosis after that interval [1]. While infected necrosis is tradionally regarded as a late event in the natural course of AP, it may occur early within the first 4 weeks in almost a quarter of patients (Fig. 3) [6]. Current international guidelines advocate postponement of all forms of invasive interventions in patients for infected necrosis preferably until the stage of walled-off necrosis (WON), which usually occurs about 4 weeks after disease onset [2, 3]. Conservative management with medical support is recommended to bridge the period between acute necrotic collection and the formation of walled-off necrosis [25]. However, despite maximal medical therapy, clinical decompensation occurs in a subset of patients wherein interventions become inevitable to temporize sepsis and improve clinical status. A recent international survey of a group of expert pancreatologists suggested a lack of consensus regarding the optimal

**Table 3** Indications and interventions between the two groups

| All NP patients (2010–2016) | NP patients with interventions < 4 weeks) ($n=76$) | NP patients with interventions ≥ 4 weeks ($n=117$) | *p* value |
|---|---|---|---|
| *New-onset organ failure prior to intervention* | | | |
| Acute kidney injury (AKI) | 33 (43.4%) | 37 (31.6%) | 0.095 |
| AKI requiring dialysis | 13 (17.1%) | 10 (8.6%) | 0.073 |
| Acute respiratory failure needing mechanical ventilation | 31 (40.8%) | 26 (22.2%) | **0.005** |
| Hypotension needing vasopressors | 10(13.2%) | 5(4.2%) | **0.03** |
| *Primary indications for intervention* | | | |
| Infection | 69 (90.8%) | 46 (39.3%) | **0.045** |
| Gastric outlet obstruction | 4 (5.3%) | 15 (12.8%) | 0.70 |
| Biliary tract obstruction | 2 (2.6%) | 5 (4.3%) | 0.522 |
| Abdominal pain | 0 | 45 (38.5%) | - |
| Other indications[a] | 1 (1.3) | 6 (5.1%) | Reference |
| Median days from AP presentation to intervention (IQR) | 20 (13–24) | 78 (42–178) | **<0.0001** |
| Initial intervention at outside center vs. our center | 12 (15.8%) vs. 64 (84.2%) | 10 (8.6%) vs.107 (91.4%) | 0.122 |
| *Initial intervention* | | | |
| Endoscopic transluminal drainage | 47 (61.8%) | 90 (76.9%) | 0.459 |
| Percutaneous drainage | 22 (28.9%) | 16 (13.7%) | 0.467 |
| Endo and perc drainage | 2 (2.6%) | 5 (4.3%) | 0.477 |
| Surgical necrosectomy | 5 (6.6%) | 6 (5.1%) | Reference |
| *Subsequent/adjuvant intervention* | | | |
| Endoscopic transluminal necrosectomy (median/range) | 1 (0–5) | 1 (0–7) | **0.118** |
| Adjuvant percutaneous drain | 32 (42.1%) | 25 (21.4%) | **0.002** |
| Sinus tract endoscopy | 4 (5.3%) | 4 (3.4%) | 0.714 |
| VARD | 6 (7.9%) | 2 (1.7%) | 0.059 |
| Open necrosectomy | 5 (6.9%) | 1 (0.9%) | 0.036 |

*IQR* interquartile range, *AP* acute pancreatitis, *AKI* acute kidney injury, *VARD* video-assisted retroperitoneal debridement
[a]Other indications—Abdominal compartment syndrome 1 for ANC and Disconnected duct 1, Failure to thrive 4, other 1 for WON
Bold values represent *p*-values which were significant and hence important

timing of interventions under these circumstances [26]. Percutaneous drainage has historically been favored for early drainage due to an expected lower risk of cavity rupture and peritoneal contamination [25]. The paucity of data on the safety of endoscopic drainage with or without necrosectomy in the early stages of necrotizing pancreatitis set up the context for the current study.

In our cohort of NP patients, infected necrosis was the primary indication for early intervention in most patients (91%). A substantial number of these patients had new-onset of organ failure or shock that was refractory to medical management. All patients had clinical deterioration prompting a multi-disciplinary decision that further delay in intervention could not be justified. Initial intervention involved endoscopic transluminal drainage as the first step in the majority (62% in early vs. 77% in the standard group).

Organ failure in AP is related to the presence of infection and the extent of necrosis [27, 28]. A recent large retrospective study showed that mortality due to primary organ failure from AP per se was relatively higher than secondary organ failure due to infected necrosis (49.5% vs. 36%, $p=0.06$). Drainage of infected fluid or necrotic collections (with or without necrosectomy) provides a window of opportunity to temporize sepsis and resultant secondary organ failure [29]. In our study, utilizing an endoscopically based step-up approach when feasible, there was substantial improvement in organ dysfunction after early as well as conventionally timed interventions. A majority of patients were successfully weaned off pressor support, mechanical ventilation, and dialysis. These findings are consistent with the PENGUIN trial and retrospective studies showing that endoscopic intervention is associated with a reduction in inflammatory response and new-onset organ failure [13, 30]. A meta-analysis of 14 observational studies showed that organ failure was associated with mortality in 30% of patients with infected necrosis, and with worse outcomes when associated with organ failure [31]. The mortality in the early intervention group in the current study was 13%, which is relatively low by comparison [14, 29]. The reduction of organ failure following

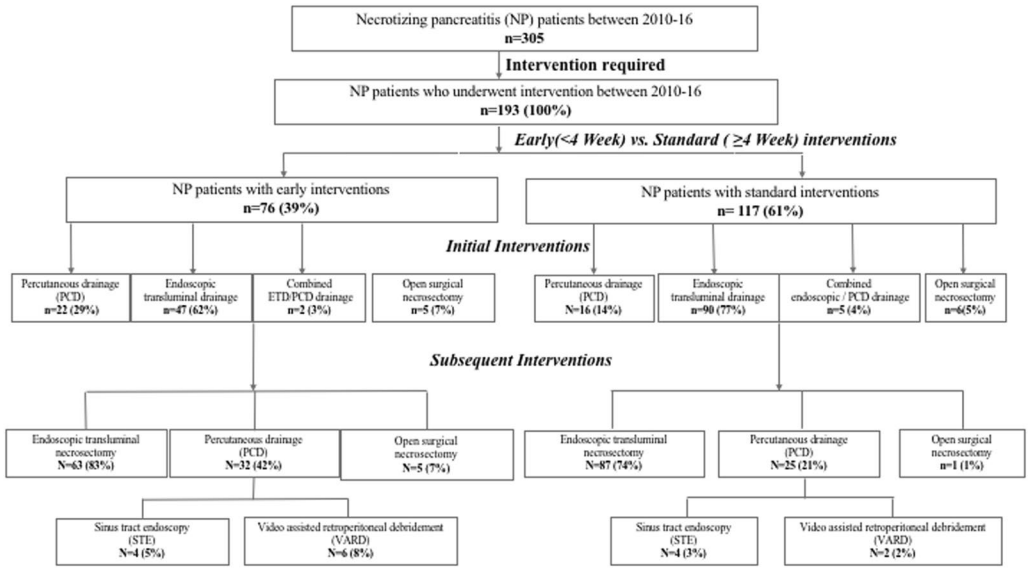


**Fig. 1** Algorithm used for multi-disciplinary interventions for necrotizing pancreatitis [5]

endoscopic step-up approach is thus clinically relevant since organ dysfunction is one of the determinants of long-term morbidity and death following pancreatitis [32].

In this study, an early endoscopic centered step-up approach to the management of necrotizing pancreatitis was found to be associated with similar outcomes to cases treated after the traditionally-recommended 4-week delay. In all cases, intervention was clearly indicated, with infection the leading indication. Although there an increase in mortality (13% vs. 4%) and need for rescue open surgery (7% vs. 1%) in those undergoing early versus standard intervention, there was no increased risk of complications. Our findings suggest that the traditional 4-week waiting period is somewhat arbitrary, and that early endoscopic based step-intervention is feasible if strongly indicated in the setting of clinical decompensation. The outcomes are likely to be optimal when performed in a multidisciplinary tertiary care setting with prompt back-up available as needed in the event of a complication, or failure to respond,

The all-cause mortality in our cohort of patients undergoing interventions for necrotizing pancreatitis was 7.8 % (15/193), which is substantially lower than the 15–39% mortality suggested in the overall literature, and somewhat lower than mortality reported in recent prospective randomized trials of minimally invasive or endoscopic interventions [2, 9, 13, 14]. It is possible that the endoscopically based step-up approach, by blunting the inflammatory response, improves organ function which in turn improves the overall mortality. Although, there was a somewhat

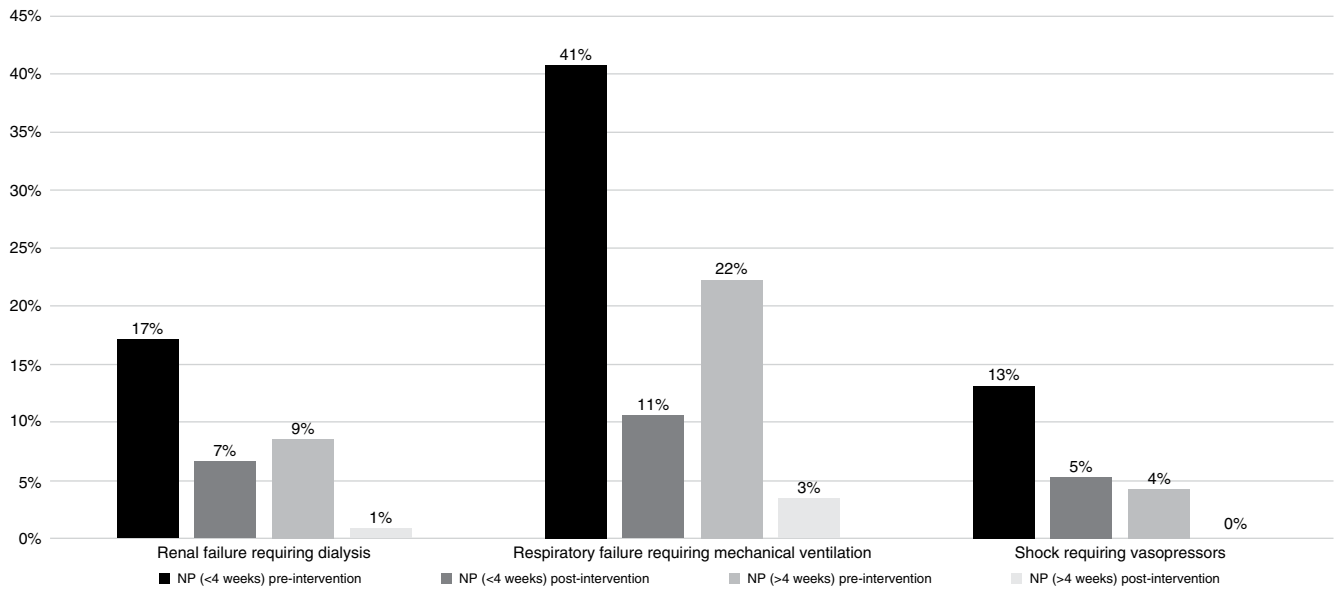


**Fig. 2** Effect of interventions on organ failure, comparing early (<4 weeks) versus standard (4 or more weeks)

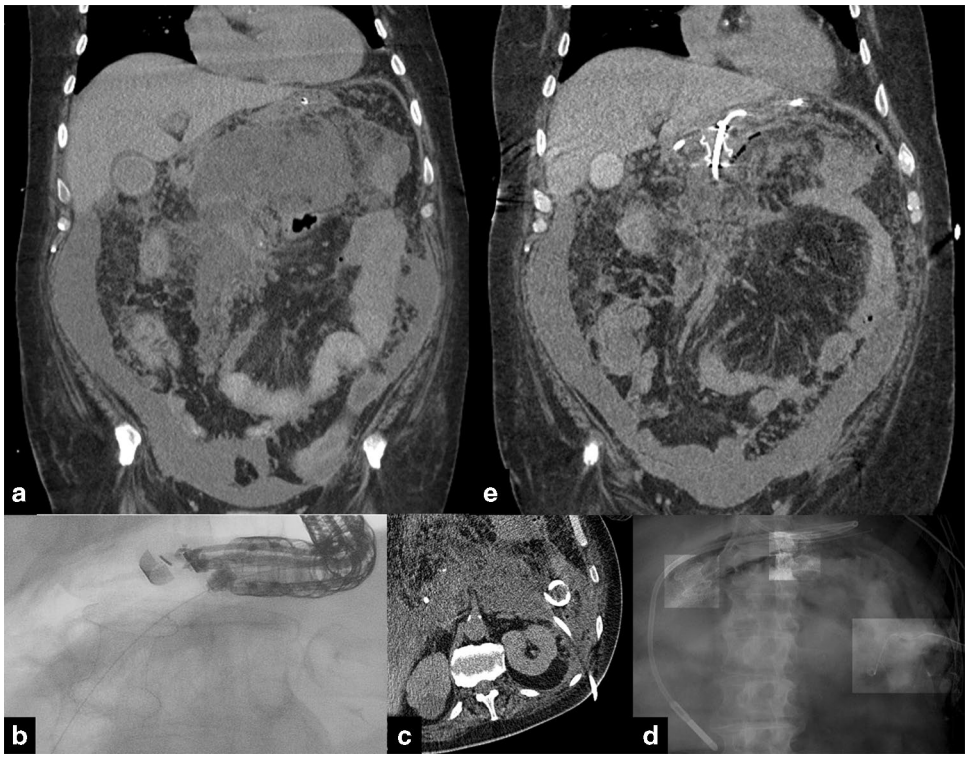


**Fig. 3** Images representing serial interventions on a 69-year-old male with severe acute pancreatitis due to gallstones, resulting in acute respiratory failure requiring mechanical ventilation and acute renal failure requiring CRRT. Three weeks after presentation, CT showed poorly demarcated acute necrotic collection with ascites (**a**); the patient decompensated further with hemodynamic instability, and underwent endoscopic transluminal drainage with lumen-apposing metallic stent (**b**), followed by left retroperitoneal percutaneous catheter drainage (**c**), with resolution of hemodynamic instability and decrease to intermittent hemodialysis; after endoscopic transluminal necrosectomy and placement of second transgastric lumen-apposing metallic stent (**d**), repeat CT showed significant decrease in size and extent of acute necrotic collection (**e**)

increased mortality in necrotizing pancreatitis after interventions before versus at or more than 4 weeks (13% vs. 4%), as well as increased lengths of ICU and hospital stay, the difference in outcomes likely reflects severity of illness rather than complications of interventions. To evaluate whether a 3-week cutoff would be more significant than the traditional 4-week cutoff, a sensitivity analysis was further performed. 43 patients underwent interventions before 3 weeks and 146 patients underwent interventions at or after 3 weeks. Not surprisingly, there was an increased mortality in the group who underwent interventions before 3 weeks (19% vs. 5%, $p = 0.003$), and increased length of hospital stay (median 40, IQR (24–70) days) vs. (median 30, IQR (16–44) days). It was still comparable to the recent prospective trials of interventions at all intervals, and a pooled international analysis of 1980 cases of minimally invasive and endoscopic versus open necrosectomy for necrotizing pancreatitis [9, 13–15].

Procedure-related complications did not differ after early compared with standard timing of intervention (Table 4). This was surprising, as early endoscopic intervention, particularly when the necrotic cavity is not adherent to the stomach or duodenum, would be anticipated to cause more perforation, cavity leakage, and peritoneal contamination. The majority of initial endoscopic transluminal drainages utilized lumen-apposing metallic stents once they became available, which could be postulated to reduce risk, but the type of stent affected neither complications nor ultimate outcome (Table 5). This finding is in keeping with data from other centers with perhaps only a trend towards less need for transluminal necrosectomy [33–36]. Somewhat surprisingly, early intervention did not result in an increased risk of cavity leakage and peritoneal contamination, with the only cases of perforation occurring after the traditional 4-week maturation period. In contrast to most other studies, the majority of our patients failed to respond adequately to minimally invasive drainage alone (early vs. standard: 78% versus 68%) and required endoscopic transluminal and /or sinus tract necrosectomy to achieve clinical response and resolve necrotic collections.

The current study provides data comparing the outcomes of an endoscopically step-up approach initiated before versus 4 or more weeks for collections associated with necrotizing pancreatitis. Our findings suggest that interventions need not necessarily be delayed until the arbitrary cut-off period of 4 weeks, especially in the setting of clinical deterioration and multi-organ failure suggesting infection. Likewise, our findings suggest that an urgent need for intervention earlier than 4 weeks does not preclude successful endoscopically based management and does not mandate percutaneous or surgical intervention. Recommendations for delayed intervention stem primarily from studies in the era of open necrosectomy involving surgical debridement of unorganized collections, which was not just technically challenging, but associated

with complications and immense physiologic stress resulting in worsened organ failure [37–40]. It is unclear if these recommendations are relevant in the era of advanced expertise and experience in endoscopic transluminal drainage and necrosectomy. Since there is no clear evidence to suggest superiority for postponed percutaneous drainage, the Dutch Pancreatitis Study Group has embarked on a randomized controlled trial (the POINTER trial—ISRCTN33682933) comparing immediate and delayed primary percutaneous drainage until there is walled-off necrosis [25, 26]. The results of this landmark study are expected to shed further insight regarding the ideal timing of primary percutaneous drainage. Similar prospective multi-center studies regarding timing of endoscopic transluminal drainage are needed to further validate our conclusions regarding endoscopically centered approaches.

There are some potential strengths and a number of limitations to the current study. A potential strength is that it is based on a prospectively maintained database of all patients admitted to the hospital with necrotizing pancreatitis of any extent—and as such it may be the first study of endoscopic interventions to represent the entire spectrum of patients rather than a case series pre-selected for suitability and perhaps high feasibility of successful endoscopic management. However, it was a single center study, and the outcomes were analyzed retrospectively. The results may not be generalizable, as all patients were managed at a single tertiary center, mostly after referral from a wide range of outside hospitals, and by a highly-specialized multi-disciplinary team with extensive experience and expertise in the entire spectrum of interventions for necrotizing pancreatitis.

In conclusion, an endoscopically centered step-up approach in necrotizing pancreatitis may be utilized earlier than 4 weeks in the setting of severe necrotizing pancreatitis with infection refractory to medical management. The outcomes of earlier intervention appear to be similar the outcomes obtained after the typically-recommended 4-week delay. Further multi-center prospective studies are needed to validate the conclusions of our study.

**Table 4 Outcomes and complications of interventions**

| Outcomes | NP patients with interventions < 4 weeks (usually ANC collections) ($n=76$) | NP patients with interventions ≥ 4 weeks (usually WON collections) ($n=117$) | *p* value |
|---|---|---|---|
| Mortality (%) | 10 (13.2%) | 5 (4.3%) | 0.024 |
| Morbidity (%) | | | |
| [a]Median length of stay in days (IQR) | 37 (27–61) | 26 (0–207) | **<0.001** |
| [b]Median length of ICU stay in days (IQR) | 2.5 (0–22) | 0 (0–3) | **<0.001** |
| *Complications (procedure and disease related)* | | | |
| Stent occlusion and infection | 30(40%) | 39(33%) | 0.36 |
| Bleeding | 8 (10.5%) | 12 (10.3%) | 0.95 |
| Perforation | 0 | 7 (6.0%) | **0.044** |
| Fistulae (including pancreatic-, cyst-, or entero-cutaneous | 25 (32.9%) | 24 (20.5%) | 0.054 |
| New-onset diabetes | 15 (19.7%) | 25 (21.4%) | 0.785 |

[a]range (ANC—min 6, max 319; WON—min 0, max 207)
[b](ANC—min 0, max 319; WON—min 0, max 186)
Bold values represent *p*-values which were significant and hence important

## CONFLICT OF INTEREST

**Guarantor of the article:** Shawn Mallery, MD.

**Potential competing interests:** M.L.F. is a consultant for Boston Scientific and Cook Medical. M.A. is a consultant for Boston Scientific. S.K.A is a consultant for Boston Scientific, US Endoscopy, Neometrics, Merit Endoscopy, and a research collaborator with Cook Medical. S.M. is a consultant for Boston Scientific. The remaining authors declare that they have no conflict of interest.

**Specific author contributions:** G.T. and S.Ma. played a role

**Table 5 Outcomes by type of transluminal stents used for initial drainage**

| Outcome | Early intervention (<4 weeks) Type of stent | | | Standard intervention (≥ 4 weeks) Type of stent | | | *p* value |
|---|---|---|---|---|---|---|---|
| | Plastic $N=41$ | Lumen apposing $N=27$ | Other metal $N=8$ | Plastic $N=57$ | Lumen apposing $N=38$ | Other metal $N=20$ | |
| Mortality | 6 (14.6%) | 2 (7.4%) | 2 (25.0%) | 2 (3.5%) | 0 | 2 (10.0%) | >0.05 |
| Hospital LOS (median, IQR) | 37 (29–62) | 35 (25–60) | 34 (22–58) | 22 (11–41) | 26 (13–55) | 29 (17–38) | >0.05 |
| ICU LOS (median, IQR) | 6 (0–26) | 0 (0–15) | 10 (0–22) | 0 (0–1) | 0 (0–5) | 0 (0–5) | >0.05 |
| Complications | | | | | | | |
| Perforation | 0 | 0 | 0 | 4(7%) | 2(5%) | 1(5%) | **<0.05** |
| Stent occlusion and infection | 16 (39.0%) | 14 (51.9%) | 4 (40.0%) | 17 (29.8%) | 15 (39.5%) | 6 (30.0%) | >0.05 |
| Fistulae (including pancreatic-, cyst-, or entero-cutaneous) | 16 (39.0%) | 7 (25.9%) | 2 (25.0%) | 14 (24.6%) | 7 (18.4%) | 3 (15.0%) | >0.05 |

Bold values represent *p*-values which were significant and hence important

in planning and/or conducting the study, collecting and/or interpreting data, and/or drafting the manuscript. P. T. played a role in planning and/or conducting the study, collecting and/or interpreting data. S.A., M.A., R.A., G.B., and S.F. played a role in planning and/or conducting the study. S.Mu. was involved in collecting and/or interpreting data. M.F. played a role in planning and/or conducting the study and drafting the manuscript.

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## REFERENCES


1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
2. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13:e1–15.
3. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400–15. 1416
4. Freeman ML, Werner J, Santvoort HCvan, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas. 2012;41:1176–94.
5. Trikudanathan G, Attam R, Arain MA, et al. Endoscopic interventions for necrotizing pancreatitis. Am J Gastroenterol. 2014;109:969–81. quiz 982
6. Petrov MS, Chong V, Windsor JA. Infected pancreatic necrosis: not necessarily a late event in acute pancreatitis. World J Gastroenterol. 2011;17:3173.
7. Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. N Engl J Med. 2016;375:1972–81.
8. Santvoort HC, van, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011;141:1254–63.
9. Santvoort HC, van, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362:1491–502.
10. Bang JY, Holt BA, Hawes RH, et al. Outcomes after implementing a tailored endoscopic step-up approach to walled-off necrosis in acute pancreatitis. Br J Surg. 2014;101:1729–38.
11. Costa DW, da, Boerma D, Santvoort HCvan, et al. Staged multidisciplinary step-up management for necrotizing pancreatitis. Br J Surg. 2014;101:e65–79.
12. Brunschot S, van, Grinsven J, van, Voermans RP, et al. Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711]. BMC Gastroenterol. 2013;13:161.
13. Bakker OJ, Santvoort HC, van, Brunschot Svan, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307:1053–61.
14. Brunschot S, van, Grinsven J, van, Santvoort HCvan, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet. 2018;391:51–58.
15. Brunschot S, van, Hollemans RA, Bakker OJ, et al. Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis: a pooled analysis of individual data for 1980 patients. Gut. 2018;67:697–706.
16. Hollemans RA, Bollen TL, Brunschot Svan, et al. Predicting success of catheter drainage in infected necrotizing pancreatitis. Ann Surg. 2016;263:787–92.
17. Babu RY, Gupta R, Kang M, et al. Predictors of surgery in patients with severe acute pancreatitis managed by the step-up approach. Ann Surg. 2013;257:737–50.
18. Raraty MGT, Halloran CM, Dodd S, et al. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. Ann Surg. 2010;251:787–93.
19. Gomatos IP, Halloran CM, Ghaneh P, et al. Outcomes from minimal access retroperitoneal and open pancreatic necrosectomy in 394 patients with necrotizing pancreatitis. Ann Surg. 2016;263:992–1001.
20. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. Ann Surg. 2000;232:175–80.
21. Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland. et al. UK guidelines for the management of acute pancreatitis. Gut. 2005;54:iii1–9.
22. Cotton PB, Eisen G, Romagnuolo J, et al. Grading the complexity of endoscopic procedures: results of an ASGE working party. Gastrointest Endosc. 2011;73:868–74.
23. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc. 2010;71:446–54.
24. Manrai M, Kochhar R, Gupta V, et al. Outcome of acute pancreatic and peripancreatic collections occurring in patients with acute pancreatitis. Ann Surg. 2016;267:357–63.
25. Grinsven J, van, Santvoort HC, van, Boermeester MA, et al. Timing of catheter drainage in infected necrotizing pancreatitis. Nat Rev Gastroenterol Hepatol. 2016;13:306–12.
26. Grinsven J, van, Brunschot S, van, Bakker OJ, et al. Diagnostic strategy and timing of intervention in infected necrotizing pancreatitis: an international expert survey and case vignette study. HPB. 2016;18:49–56.
27. Garg PK, Madan K, Pande GK, et al. Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. Clin Gastroenterol Hepatol. 2005;3:159–66.
28. Isenmann R, Rau B, Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. Br J Surg. 1999;86:1020–4.
29. Padhan RK, Jain S, Agarwal S, et al. Primary and secondary organ failures cause mortality differentially in acute pancreatitis and should be distinguished. Pancreas. 2018;47:302–7.
30. Kumar N, Conwell DL, Thompson CC. Direct endoscopic necrosectomy versus step-up approach for walled-off pancreatic necrosis. Pancreas. 2014;43:1334–9.
31. Petrov MS, Shanbhag S, Chakraborty M, et al. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology. 2010;139:813–20.
32. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut. 2004;53:1340–4.
33. Siddiqui AA, Kowalski TE, Loren DE, et al. Fully covered self-expanding metal stents versus lumen-apposing fully covered self-expanding metal stent versus plastic stents for endoscopic drainage of pancreatic walled-off necrosis: clinical outcomes and success. Gastrointest Endosc. 2017;85:758–65.
34. Sharaiha RZ, Tyberg A, Khashab MA, et al. Endoscopic therapy with lumen-apposing metal stents is safe and effective for patients with pancreatic walled-off necrosis. Clin Gastroenterol Hepatol. 2016;14:1797–803.
35. Bang JY, Hasan M, Navaneethan U, et al. Non-superiority of lumen-apposing metal stents over plastic stents for drainage of walled-off necrosis in a randomised trial. Gut 2018 (epub ahead of print).
36. Brimhall B, Han S, Tatman PD, et al. Increased incidence of pseudoaneurysm bleeding with lumen-apposing metal stents compared to double-pigtail plastic stents in patients with peripancreatic fluid collections. Clin Gastroenterol Hepatol. 2018; (epub ahead of print).
37. Mier J, León EL, Castillo A, et al. Early versus late necrosectomy in severe necrotizing pancreatitis. Am J Surg. 1997;173:71–75.
38. Besselink MGH, Verwer TJ, Schoenmaeckers EJP, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg. 2007;142:1194–201.
39. Horvath K, Freeny P, Escallon J, et al. Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections: a multicenter, prospective, single-arm phase 2 study. Arch Surg. 2010;145:817–25.
40. Rodriguez JR, Razo AO, Targarona J, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. Ann Surg. 2008;247:294–9.