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The effect of a novel minimally invasive strategy for infected necrotizing pancreatitis

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Abstract
Background Step-up approach consisting of multiple minimally invasive techniques has gradually become the mainstream for managing infected pancreatic necrosis (IPN). In the present study, we aimed to compare the safety and efficacy of a novel four-step approach and the conventional approach in managing IPN.
Methods According to the treatment strategy, consecutive patients fulfilling the inclusion criteria were put into two time intervals to conduct a before-and-after comparison: the conventional group (2010–2011) and the novel four-step group (2012–2013). The conventional group was essentially open necrosectomy for any patient who failed percutaneous drainage of infected necrosis. And the novel drainage approach consisted of four different steps including percutaneous drainage, negative pressure irrigation, endoscopic necrosectomy and open necrosectomy in sequence. The primary endpoint was major complications (new-onset organ failure, sepsis or local complications, etc.). Secondary endpoints included mortality during hospitalization, need of emergency surgery, duration of organ failure and sepsis, etc.
Results Of the 229 recruited patients, 92 were treated with the conventional approach and the remaining 137 were managed with the novel four-step approach. New-onset major complications occurred in 72 patients (78.3%) in the two-step group and 75 patients (54.7%) in the four-step group ($p < 0.001$). For other important endpoints, although there was no statistical difference in mortality between the two groups ($p = 0.403$), significantly fewer patients in the four-step group required emergency surgery when compared with the conventional group [14.6% (20/137) vs. 45.6% (42/92), $p < 0.001$]. In addition, stratified analysis revealed that the four-step approach group presented significantly lower incidence of new-onset organ failure and other major complications in patients with the most severe type of AP.
Conclusion Comparing with the conventional approach, the novel four-step approach significantly reduced the rate of new-onset major complications and requirement of emergency operations in treating IPN, especially in those with the most severe type of acute pancreatitis.

Keywords Infected pancreatic necrosis · Minimally invasive · Negative pressure irrigation · Endoscopic necrosectomy · Stratified analysis

In patients with acute pancreatitis (AP), a certain proportion of them would develop secondary infection, namely infected pancreatic necrosis (IPN), in the later course of the disease. It is reported that IPN is an independent determinant for mortality and morbidity, leading to poor prognosis

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[1]. Also, it is strongly recommended that proactive intervention combined with antibiotic treatment is necessary in those patients with IPN [2].

Open necrosectomy (ON) was once regarded as the primary choice for IPN. However, this invasive procedure is reported to be associated with high mortality (11–39%) and morbidity (34–95%) [3–7] as well as long-term pancreatic dysfunction. Thus, minimally invasive techniques, including percutaneous catheter drainage (PCD), transgastric endoscopic debridement (TED) and video-assisted retroperitoneal debridement (VARD), have emerged since decades ago [8–12]. Recently, step-up approaches combining these new techniques in sequence have shown promising results in reducing morbidity and mortality of the IPN patients [12–18]. In this way, minimally invasive approaches seem to gradually replace the traditional position of ON and become the mainstream of IPN therapy.

Complying with the international trend, IPN therapy in our center was also improved during the past years. ON had always been the main way for IPN patients before 2008. Meanwhile, PCD was also performed in a certain part of AP patients, mostly to make a definite diagnosis of IPN, although a few patients could be cured unexpectedly after that. PCD has gradually become the first choice for IPN patients since 2008 and approximate half of the IPN patients could fully recover with PCD alone. While, most of the IPN patients with high computed tomography (CT) density and wide distribution of pancreatic necrosis were converted to operation. We also attempted TED or VARD for managing these patients during the past few years. Whereas, no favorable results were achieved, which might owe to the lack of experience. All of the above situations promoted the development of our novel step-up strategy.

As our department was a transfer center for intestinal fistula in China, we have accumulated rich experience in the management of peritoneal/retroperitoneal infection. Among which, continuous negative pressure irrigation (CNPI) in the abscess via a double catheterization cannula is one of the key techniques. Before 2012, we only insert the double catheterization cannula during the procedure of ON for postoperative CNPI. With the improvement in minimally invasive techniques, we can dilate the sinus created by PCD using the Seldinger technique and then insert the double catheterization cannula for CNPI. Furthermore, through the sinus tract created by the double catheterization cannulas, we can use an electronic gastroscope (30F) for endoscopic necrosectomy (ED). After all these minimally invasive therapy, only few patients required ON. And this distinctive four step-up approach, which has never been applied in other centers, has become the primary way for IPN therapy in our center since 2012.

In the present study, we aimed to compare the safety and clinical efficiency of the novel four step-up approaches and the conventional two step-up approaches among patients with IPN.

Methods

We conducted a before-and-after study with a prospectively collected database at the Department of General Surgery of Jinling Hospital, Nanjing University between January 2010 and December 2013. During the study period, all the consecutive patients admitted to our center with a diagnosis of IPN were registered in an internal database and screened for potential enrollment. The study was approved by the Institutional Review Board of Jinling Hospital. The inclusion criteria for the study were: (1) patients with a confirmed diagnosis of AP based on the Atlanta Criteria [19]; (2) aged between 18 and 70 years old; and (3) developed IPN during the clinical course (according to the presence of gas bubbles within pancreatic necrosis on CT scan or a positive bacterial culture obtained by fine-needle aspiration, first drainage and/or operation [20]). Patients were excluded if they met one or more following criteria: (1) they were in pregnancy, with malignancy or auto-immune diseases, etc.; (2) they had received exploratory laparotomy for necrosectomy, abdominal compartment syndrome (ACS), perforation of a visceral organ, intra-abdominal bleeding, etc., in other hospitals before admitting to our institute during the current episode of AP; (3) they had received intervention for IPN in other hospitals before admitting to our institute during the current episode of AP; (4) the treatment strategy was not completed owing to nonmedical reasons. Initial medical treatment was carried out for every patient before IPN confirmation according to the international recommendations [21, 22]. Baseline characteristics such as acute physiology and chronic health evaluation (APACHE) II score, CT severity index, sequential organ failure assessment (SOFA) score and body mass index (BMI) were evaluated and collected on admission. Laboratory data including C-reactive protein (CRP), albumin and white blood cells (WBC) were also assessed within 24 h after admission.

Definitions

The severity of pancreatitis was assessed and classified before intervention according to the revised Atlanta classification [2]. New-onset complication was defined as the development of a complication that was not present at any time during the last 24 h before the first intervention [12].

Organ functions were evaluated in three organ systems: cardiovascular, renal and respiratory systems. The criteria for cardiovascular, renal and respiratory failure were defined based on recently published international consensus [2, 20]: cardiovascular (systolic blood pressure <90 mmHg despite adequate fluid resuscitation or need for inotropic agent), renal [serum creatinine ≥171 μmol/L (2.0 mg/dL) after rehydration] and respiratory [$PaO2/FiO2 \leq 300$ mmHg (40 kPa)]. Multiple organ failure (MOF) was defined as the failure on two or more systems at the same time. Organ failure presenting for <48 h was defined as transient organ failure and presenting for >48 h was defined as persistent organ failure [2].

The definition of sepsis and septic shock was based on the international consensus of surviving sepsis campaign (SSC) 2012 [23]. ACS was defined as a sustained intra-abdominal pressure (IAP) >20 mmHg [with or without an abdominal perfusion pressure (APP) <60 mmHg] that was associated with new organ dysfunction/failure according to the updated consensus of World Society of the Abdominal Compartment Syndrome (WSACS) [24]. Gastrointestinal fistula was defined as the discharge of the contents of gastric, small or large bowel from a drain or from the surgical wound [16]. Intra-abdominal bleeding was defined as peritoneal/retroperitoneal bleeding that required surgical, radiologic or endoscopic intervention. Gastrointestinal bleeding was defined as all forms of bleeding in the gastrointestinal tract, from the mouth to the rectum and blood loss more than 500 ml/24 h.

Minimally invasive techniques

Conventional two-step approach (2010–2011)

Step one: PCD Image-guided PCD was well described in our previous study [25, 26]. All drainages were performed under the guidance of ultrasound or CT using the Seldinger technique. First, percutaneous needle was inserted into the IPN, avoiding the adjacent vital organs. After that, the catheter tract was dilated and a pigtail catheter (Bioteque Corporation, Taiwan, China) was inserted. After necrotic sample was acquired for bacterial culture, all the liquefied necrotic tissue was aspirated. Irrigation was started the next day with 0.9% saline solution every 4 h. Assessment should be started since the third day after PCD. If the clinical symptoms of the patient were gradually improved, the irrigation should be continued. If a patient failed to show clinical improvement after 3 days, he/she should be timely converted to open necrosectomy.

Step two: ON The procedure of ON, originally described by Beger et al. [12], was similar to previous reports. Briefly, a laparotomy through a bilateral subcostal incision was performed. After complete removal of pancreatic and peri-pancreatic necrosis, several double catheterization cannulas were inserted for postoperative irrigation and the abdomen was closed.

Novel four-step approach (2012–2013)

Different from the conventional two-step approach, the novel four-step approach for the patients admitted during the period from January 2012 to December 2013 including the following four procedures: PCD, CNPI, ED and ON in sequence. The detailed technique procedure and indications for each step of this strategy were described in the attached file and more details could be seen in our previous report [27].

Step one: PCD

The procedure of PCD was described above. When one or more of the following criteria was met: (1) clinical improvement (improved organ function including cardiovascular, respiratory and renal or at least 10% drop of APACHE II score) was not achieved with PCD alone in 3 days after procedure or CT results showed the drain was inadequate, (2) mean CT density of necrotic tissue was above 30Hu or (3) suspected or diagnosed gastrointestinal fistula, the second step would be applied.

Step two: CNPI

Irrigation was performed through a "double catheterization cannula" of size 24–30F (Figs. 1, 2). The procedure of cannula catheterization was similar to that of PCD under the guidance of ultrasound or CT. In patients who received CNPI, PCD would usually be additionally applied to construct a "drainage system" (Fig. 3) to facilitate the drainage.

Step three: ED

ED was applied following NPI when necessary before consideration of ON. An electronic gastroscope of 30F was used in the procedure of ED. The gastroscope could get through the man-made sinus tract created by "double catheterization cannula" and drag out solid necrotic tissue, which could not be rinsed out by PCD or CNPI, with the help of a snare.

Step four: ON

The procedure of ON was also described above.

During any procedure of the four-step strategy, if patients suffered one or more of the following situation: (1) intra-abdominal bleeding could not be controlled by conservative treatment or interventional embolization; (2) ongoing ACS

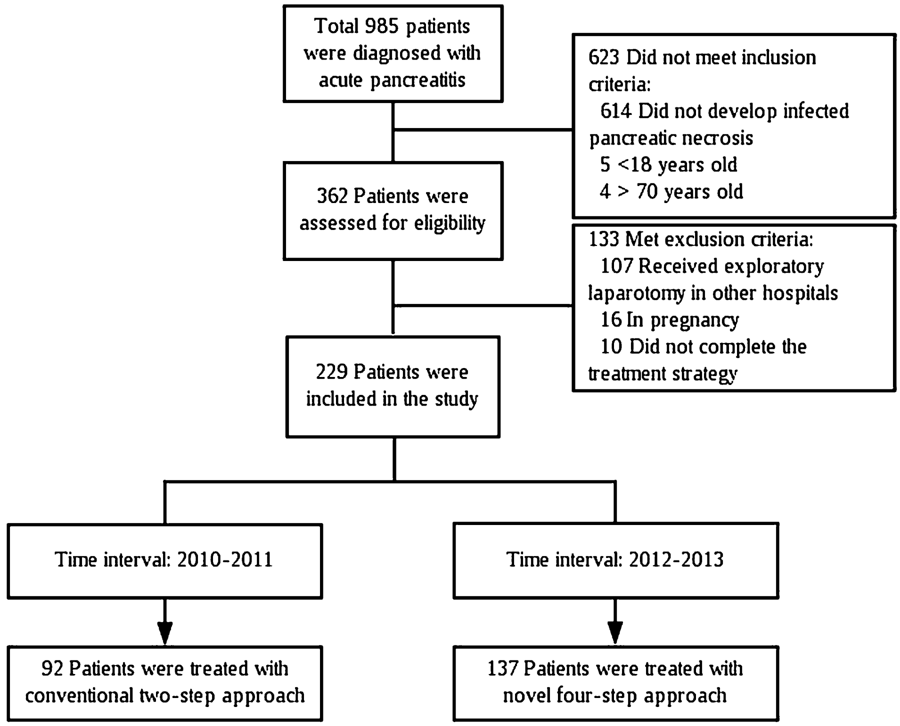

Fig. 1 Screening and enrollment of the study patients

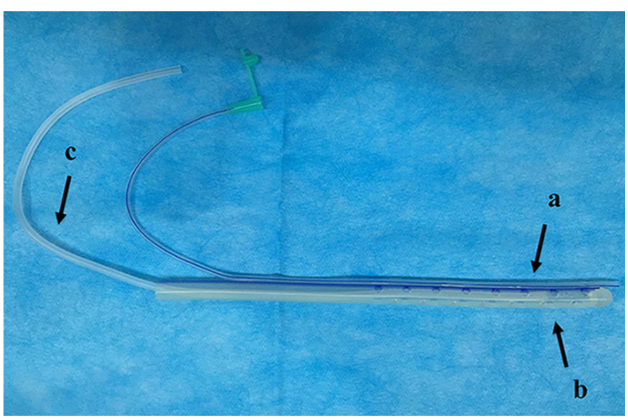

Fig. 2 Picture of double catheterization cannula. The double catheterization cannula is made of three parts: Part *A* is a 8F plastic tube for continuous infusion of normal saline. Part *B* is a 24–30F-in-diameter dead-end plastic tube. Part *C*, which is used for continuous negative pressure drainage, is a plastic catheter inside part *B*

which could not be alleviated by conservative management; (3) progression of septic shock; (4) confirmed gastrointestinal fistula could not be well drained by PCD or CNPI (depending on the judgment of the treating physician); they would be converted to emergency ON.

All the procedures were performed by the same medical team (including two physicians, six gastrointestinal surgeons, three endoscopists and two radiologists) who were experienced in pancreatic surgery as well as other procedures.

Data collection and endpoints

Demographic data including age, gender, etiology, comorbidities, APACHE II score and SOFA score before intervention, time interval from AP onset to admission and from IPN diagnosis to intervention of all study patients were recorded and collected. CECT was performed on admission, before discharge and on demand of the treating physician. The extent of the pancreatic necrosis was measured according to the image findings, and the CT severity index was assessed based on the Balthazar's CT score [28].

Patients were discharged after clinical recovery with/without drainage catheters in situ. All the patients were followed up for at least 6 months after discharge as outpatients in the clinic, with a frequency of every 2 weeks for the first 2 months and monthly for the following 4 months. The drainage catheter would not be removed until (1) disappearance of clinical symptom with no recurrence; (2) the output of the catheter was less than 5 ml/d for 7 consecutive days; and (3) CT scan confirmed no residual collection.

The primary endpoint was major complications (new-onset organ failure, sepsis or local complications including intra-abdominal bleeding, gastrointestinal bleeding and gastrointestinal fistula required intervention). The secondary endpoints included hospital mortality, need of emergency surgery, duration of organ failure and sepsis, ICU re-admission after discharge, other AP-related

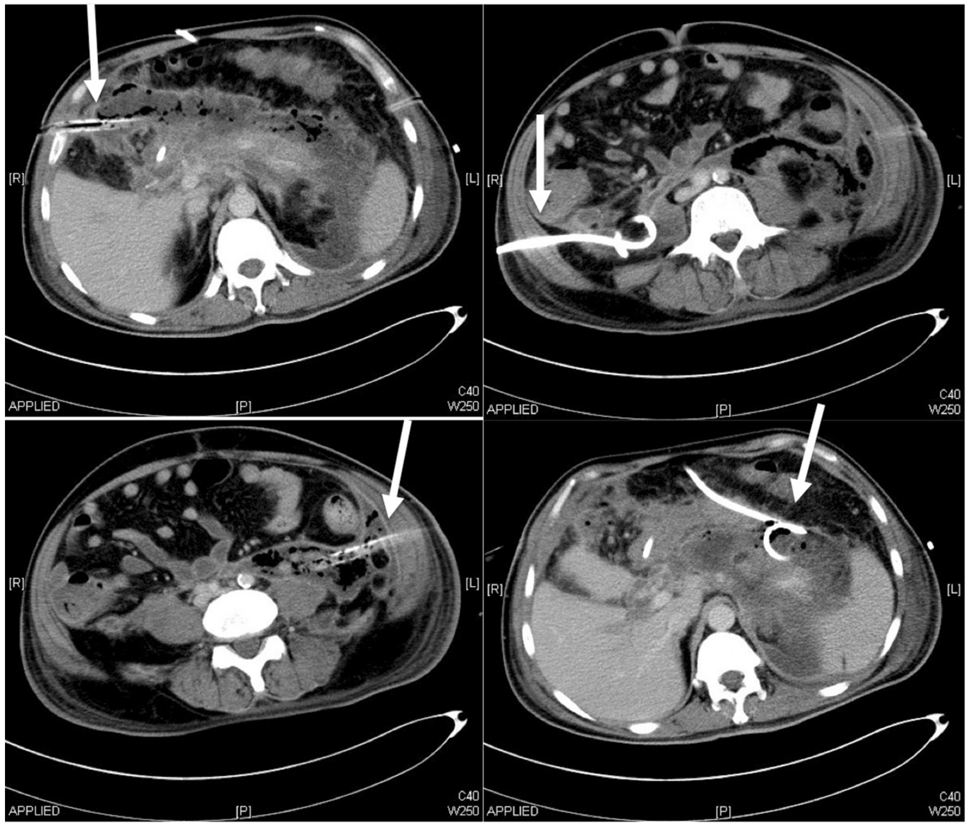

Fig. 3 Samples for the "drainage system" consisting of pigtail catheter and double catheterization cannula (*white arrow*)

complications, exacerbations of pre-existing comorbidities, length of hospital and ICU stays and economical cost, etc.

Stratified analysis

The patients were divided into two subgroups according to the presence of organ failure: (1) moderately severe AP: IPN patients without persistent organ failure, (2) severe AP: IPN patients with persistent organ failure. Major complications (including new-onset organ failure, intra-abdominal bleeding and gastrointestinal fistula), mortality, length of hospital and ICU stays as well as cost were compared and analyzed between patients receiving the two different strategies in each subgroup.

In addition, patients who underwent operation in the two groups were also compared in terms of reason for primary operation, incidence of postoperative complications (including new-onset organ failure, intra-abdominal bleeding and gastrointestinal fistula) as well as postoperative mortality.

Statistically analysis

Continuous variables were expressed as medians plus interquartile ranges (IQR) or range due to the variability of the study patients. Categorical variables were described in absolute numbers and in percentages. All the statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) 22.0 statistical software package (IBM Analytics, Armonk, NY) in our study. For continuous variables, after checking normality using Kolmogorov–Smirnov test, student t test was applied for normally distributed data and the Mann–Whitney *U* test for skewed data to compare the means. For comparison of categorical variables, Chi-square or Fisher's exact test was applied. Results were presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). All p values were two-sided, and a p value of <0.05 was considered statistically significant.

Results

Study participants

During the study period from January 2010 to December 2013, a total of 229 patients with IPN were enrolled in this study. Ten patients did not complete the treatment strategy due to financial reasons, as shown in Fig. 1. Of all the enrolled patients, 92 patients (admitted between January 2010 and December 2011) were treated with the conventional two-step approach and the other 137 patients (admitted between January 2012 and December 2013) were treated with the novel four-step approach for IPN. Patients in the two treatment groups had similar demographic and clinical characteristics (Table 1). Besides, as 90% of the study patients were transferred from other hospitals, the median time from AP onset to admission was similar, around 4 weeks in both groups ($p = 0.209$). The majority of the patients presented low levels of serum albumin, high levels of serum C-reactive protein (CRP) and white blood cells (WBC) on admission. Over four fifths of the patients received enteral nutrition as the major way for nutritional support and around one-third of them required mechanical ventilation for breathing support due to respiratory failure.

Conventional two-step approach

During the study period between January 2010 and December 2011, 92 patients were treated with the conventional two-step approach for IPN. Almost one-third of the patients (31.5%, 29 of 92) suffered complete necrosis of the pancreas, of whom, thirteen cases underwent primary operative necrosectomy. Most patients in this group suffered severe AP and the CT severity index was also extremely high (Tables 1 and 2). More than half of the patients presented organ failure at admission without extremely high APACHE II score and SOFA score (Tables 1, 2), predominantly respiratory failure (51.1%, 47 of 92). Mesocolon was involved by necrosis in 33 cases (35.9%) and most of them developed colonic fistula in the late phase of the disease. Almost half of the patients developed septicemia during hospitalization, with *Escherichia coli* being the major pathogen (detailed microbiological data in Supplementary Table 1). About 44.6% (41 of 92) of the study patients received PCD only during the study period. Thirty-three patients (35.9%) underwent both PCD and ON, and the median time interval from AP onset to surgery was around 40 days (Supplementary Table 2). In addition, 51 patients (55.4%) received one or more operations during the process, of which, 42 (45.6%) patients required emergency operation for ongoing deteriorated organ functions and/or uncontrolled intra-abdominal bleeding (Table 3). Finally, 26 patients died during hospitalization. Of which, 25 died of infection-related MOF and the other one died of cerebral hemorrhage after the infection was well controlled.

Novel four-step approach

Between 2012 and 2013, 137 patients with IPN were treated with the novel four-step approach. Similar to the patients managed with the conventional approach, most patients in this group also suffered the most severe type of AP with a large extent (above 50%) of pancreatic necrosis (Table 2). Around 30% of the patients developed complete necrosis of the pancreas, of whom, 13 cases underwent ON for inadequate drainage or progression of septic shock. Lung was the most common organ involved in SAP patients (67.9%, 93 of 137) and approximately half of the patients required mechanical ventilation. A total of seven different strategies were applied in our patients and about 39.4% (54 of 137) of the study patients received PCD only. Other commonly applied strategies included PCD + NPI, PCD + ON, PCD + NPI + ED and PCD + NPI + ON. Of all the patients treated with the four-step approach, eight patients underwent all the four steps. In general, a median of two steps and three procedures were applied for each patient (Supplementary Table 2). The median time interval from AP onset to surgery was around 2 months. Comparable to the patients receiving the conventional approach, 51 patients (37.2%) in the four-step group developed septicemia during hospitalization, with *Klebsiella pneumonia* being the major pathogen (Supplementary Table 1). Eventually, 32 patients (23.4%) died during hospitalization. Of whom, 28 died of infection-related MOF, two died of massive trachea hemorrhage and the other two died of uncontrolled infection caused by toxic epidermal necrolysis and pressure sore, respectively.

Clinical endpoints

Table 3 represents with the clinical endpoints of the patients in the two groups. The primary endpoint occurred in 72 patients (78.3%) of the conventional group and 75 patients (54.7%) of the novel group (OR for four-step approach: 0.34, 95% CI 0.18–0.61, $p < 0.001$). It is obvious that patients treated with the conventional approach were more likely to develop organ failure after intervention and cardiovascular was most commonly involved. The difference was also sound in new-onset intra-abdominal bleeding and gastrointestinal fistula. The incidence of new-onset organ failure was markedly lower for the novel four-step group than the conventional group (22/137 vs. 28/92, $p = 0.010$), as well as the incidence of local complications (49/137 vs. 45/92, $p = 0.047$). Twenty-four patients (17.5%) in the four-step group and 34 patients (37.0%) in the two-step group developed intra-abdominal bleeding after intervention (OR for four-step approach: 0.36, 95% CI 0.20–0.67, $p = 0.001$). For the patients following the two-step approach, the bleeding event mainly occurred after the primary operation. Most cases of bleeding occurred in the retroperitoneum for both groups, and emergency surgery was applied in 9 cases of the two-step group and 12 cases of the four-step group. Also, more patients developed gastrointestinal fistulas in the conventional group than those in the four-step group (24/137 vs. 29/92, $p = 0.014$), mostly colonic fistula. Twelve cases of the four-step group

Table 1 Demographic data and baseline characteristics of the patients

Characteristic	Four-step group (n = 137)	Two-step group (n = 92)	p value
Age, year	46 (39, 57)	48.5 (39.5, 55.8)	0.739
Gender, male/female	91/46	64/28	0.618
BMI[a]	24.2 (21.2, 26.8)	25.0 (24.1, 27.8)	0.413
APACHE II score[b]	11 (8, 16)	12 (8, 16)	0.289
APACHE II score $\geq$20, no. (%)	19 (13.9)	14 (15.2)	0.776
CT severity index[c]	10 (8, 10)	10 (8, 10)	0.900
SOFA score[d]	3.5 (2, 5)	2 (2, 5)	0.716
Etiology of pancreatitis, no. (%)			
Biliary	68 (49.6)	44 (47.8)	0.788
Alcohol	21 (15.3)	20 (21.7)	0.215
HTG	45 (32.8)	26 (28.3)	0.462
Other	3 (2.2)	2 (2.2)	0.994
Comorbidities, no. (%)			
Cardiovascular disease[e]	39 (28.5)	33 (35.9)	0.237
Chronic lung disease	6 (4.4)	2 (2.2)	0.373
Chronic renal insufficiency	5 (3.6)	4 (4.3)	0.790
Diabetes mellitus	26 (19.0)	18 (19.6)	0.912
Nonmedical history			
Smoking	53 (38.7)	33 (35.9)	0.666
Drinking	56 (40.9)	38 (41.3)	0.948
Laboratory data			
CRP, mg/L	134 (89, 180)	142 (88, 208)	0.074
Albumin, g/L	31.2 (28.5, 34.2)	33.2 (30.5, 35.6)	0.141
WBC, *10^9/L	9.9 (7.4, 15.4)	11.0 (8.2, 16.5)	0.266
Time interval from IPN diagnosis to intervention, days	5 (1, 15.8)	6 (2.8, 13.2)	0.605
Nutritional support, no. (%)			
TEN	116 (84.7)	79 (85.9)	0.803
TPN	4 (2.9)	3 (3.3)	0.883
EN + PN	17 (12.4)	10 (10.9)	0.723
Organ supportive therapy before intervention			
Mechanical ventilation	50 (36.5)	33 (35.9)	0.923
CRRT	36 (26.3)	31 (33.7)	0.226
Vasoactive agents	15 (10.9)	10 (10.9)	0.985

Values are median ± interquartile range (IQR). *HTG* denotes hypertriglyceridemia,*CRP* C-reactive protein, *WBC* white blood cells, *TEN* total enteral nutrition, *TPN* total parenteral nutrition, *CRRT* continuous renal replacement therapy

[a] MI denotes body mass index and equals to the weight (kilograms) divided by the square of the height (meters)

[b] APACHE II score denotes scores on the Acute Physiologic and Chronic Health Evaluation II (APACHE II) scale and scores range from 0 to 71, with higher scores indicating more severe disease

[c] Scores on the CT severity index (data obtained before intervention) range from 0 to 10, with higher scores indicating more extensive pancreatic and peri-pancreatic necrosis

[d] SOFA score denotes score on the sequential organ failure assessment scale and ranges from 0 to 24, with higher scores indicating more severe organ

[e] Mainly hypertension and coronary heart disease

and 13 cases of the two-step group underwent operative ileostomy or colostomy for colonic fistula.

There was no statistical significance in the mortality rate between the two groups (32/137 vs. 26/92, OR for four-step approach: 0.77, 95% CI 0.42–1.41, p = 0.403). Moreover, patients were more likely to have a higher mortality rate after primary necrosectomy, as 18 of the 26 (69.2%) non-survivors in the conventional group and 16 of the 32

Table 2 Severity of the disease in the patients

Variable	Four-step group (n = 137)	Two-step group (n = 92)	p value
Grading of AP			0.052
Moderately severe	41 (29.9)	39 (42.4)	
Severe	96 (70.1)	53 (57.6)	
Extent of pancreatic necrosis, no. (%)			0.689
<30%	15 (10.9)	8 (8.7)	
30–50%	39 (28.5)	27 (29.3)	
>50%	83 (60.6)	57 (62.0)	
Extrapancreatic distribution[a]	7 (6, 8)	6 (5, 8)	0.264
Extrapancreatic Necrosis			
LAPR	13 (9.5)	11 (12.0)	0.550
RAPR	4 (2.9)	2 (2.2)	0.729
BAPR	41 (29.9)	23 (25.0)	0.415
RAPR + mesocolon	9 (6.6)	5 (5.4)	0.725
LAPR + mesocolon	22 (16.0)	13 (14.1)	0.691
BAPR + mesocolon + mesenteric	28 (20.4)	15 (16.3)	0.432
Disease severity, no. (%)			
SIRS[b]	137 (100)	92 (100)	–
Organ failure	96 (70.1)	53 (57.6)	0.052
ARDS	93 (67.9)	47 (51.1)	0.011
AKI	41 (29.9)	27 (29.3)	0.925
Shock	30 (21.9)	14 (15.2)	0.208
Positive blood culture before intervention	12 (8.8)	9 (9.8)	0.792

AP denotes acute pancreatitis, *LAPR* left anterior pararenal region, *RAPR* right anterior pararenal region, *BAPR* bilateral anterior pararenal region

[a] The distribution of infected necrosis included lesser sac, pancreatic head, pancreatic body, pancreatic tail, left anterior pararenal space, right anterior pararenal space, left paracolic sulci, right paracolic sulci, and pelvic cavity. Each space stands for 1 point, which sums up to 9 points [1]

[b] SIRS denotes systemic inflammatory response syndrome, which is defined according to the consensus-conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine

(50.0%) nonsurvivors in the four-step group underwent one or more operations. Forty-two patients (45.6%) in the two-step group and 20 patients (14.6%) in the four-step group needed emergency surgery (OR for four-step approach: 0.20, 95% CI 0.11–0.38, $p < 0.001$) due to ongoing deteriorated organ functions or uncontrolled intra-abdominal bleeding. Although there was no significant difference in terms of duration of organ failure between the two groups, higher incidence of exacerbated cardiovascular disease was seen in the patients treated by conventional approach (9/137 vs. 14/92, $p = 0.033$), mostly presenting with atrial fibrillation, stroke and/or heart failure. Additionally, it was notable that patients treated by the four-step approach had comparable and even shorter hospital [38.5 (IQR 21–62.5) days vs. 42 (IQR 24–73) days, $p = 0.193$] and ICU stays [19 (IOR 7–43) days vs. 28 (IQR 13–49) days, $p = 0.193$] as well as lower rate of ICU re-admission after discharge (25/137 vs. 36/92, OR for four-step approach: 0.47, 95% CI 0.30–0.72, $p < 0.001$) than those treated by conventional approach, despite the more steps and procedures they received.

Surgical intervention

Twenty-eight patients (20.4%) in the four-step group and 51 patients (55.4%) in the two-step underwent one or more operations during the clinical course of AP. Progression of septic shock was the major cause for the first operation in both groups (Tables 4, 5). Other causes included uncontrolled intra-abdominal bleeding, gastrointestinal fistula, ongoing ACS, etc. There was no significant difference in new-onset organ failure (9/28 vs. 22/51, OR for four-step approach: 0.62; 95% CI 0.24–1.64, $p = 0.338$) after the operation between the two groups. Notably, patients following the four-step approach tended toward a higher mortality rate after the operation than those following the conventional approach (16/28 vs. 18/51, OR for four-step approach: 2.44; 95% CI 0.24–1.64, $p = 0.061$), despite of reduced postoperative hospital duration and complications such as intra-abdominal bleeding and gastrointestinal fistula. This might partially blame to the overly strict indications for ON in the novel four-step approach.

Table 3 Endpoints of the patients following the two different approaches

Variable	Four-step group ($n = 137$)	Two-step group ($n = 92$)	OR (95% CI)	p value
Major complication, no. (%)[a]	75 (54.7)	72 (78.3)	0.34 (0.18–0.61)	<0.001
New-onset organ failure	22 (16.0)	28 (30.4)	0.44 (0.23–0.83)	0.010
ARDS	3 (2.2)	5 (5.4)	0.39 (0.09–1.67)	0.190
AKI	8 (5.8)	8 (8.7)	0.65 (0.24–1.80)	0.406
Shock	18 (13.1)	22 (23.9)	0.48 (0.24–0.96)	0.035
Multiple organ failure	17 (12.4)	23 (25.0)	0.50 (0.28–0.88)	0.014
New-onset complication	49 (35.8)	45 (48.9)	0.58 (0.34–1.00)	0.047
Intra-abdominal bleeding	24 (17.5)	34 (37.0)	0.36 (0.20–0.67)	0.001
Gastrointestinal bleeding	1 (0.7)	1 (1.1)	0.67 (0.04–10.83)	0.776
Gastrointestinal fistula	24 (17.5)	29 (31.5)	0.46 (0.25–0.86)	0.014
ACS	7 (5.1)	6 (6.5)	0.77 (0.25–2.38)	0.651
New-onset sepsis	26 (19.0)	23 (25.0)	0.70 (0.37–1.33)	0.276
Hospital mortality, no. (%)	32 (23.4)	26 (28.3)	0.77 (0.42–1.41)	0.403
Disease specific	30 (21.9)	25 (27.2)	0.75 (0.41–1.39)	0.360
Disease nonspecific	2 (1.4)	1 (1.1)	1.35 (0.12–15.09)	0.808
Need of emergency surgery, no. (%)[b]	20 (14.6)	42 (45.6)	0.20 (0.11–0.38)	<0.001
Need of surgery, no. (%)	28/137	51/92	0.21 (0.12–0.37)	<0.001
Duration of organ failure after intervention, days				
ARDS	6 (4, 23)	12 (6, 37)		0.292
Range	2–110	3–88		
AKI	11 (6, 25.8)	20 (8.2, 24.5)		0.992
Range	3–124	4–64		
Shock	5 (3, 10)	5 (3, 10.5)		0.665
Range	2–49	3–15		
Duration of sepsis after intervention, days	8.5 (4.8, 17.2)	9.5 (5.8, 16.8)		0.779
Range	2–49	5–52		
ICU re-admission after discharge, no. (%)	25 (18.2)	36 (39.1)	0.47 (0.30–0.72)	<0.001
Other new-onset complication, no. (%)				
Pancreatic fistula	12 (8.8)	10 (10.9)	0.79 (0.32–1.91)	0.595
Splanchnic venous thrombosis	6 (4.4)	6 (6.5)	0.66 (0.20–2.10)	0.476
New-onset diabetes mellitus	24 (17.5)	30 (32.6)	0.44 (0.24–0.82)	0.008
Exacerbation of pre-existing comorbidities, no. (%)				
Diabetes mellitus[c]	13 (9.5)	14 (15.2)	0.58 (0.26–1.31)	0.188
Cardiovascular disease[d]	9 (6.6)	14 (15.2)	0.39 (0.16–0.95)	0.033
Chronic lung disease[e]	5 (3.6)	4 (4.3)	0.83 (0.22–3.19)	0.790
Chronic renal insufficiency[f]	3 (2.2)	3 (3.3)	0.66 (0.13–3.36)	0.619
Length of ICU stay, days	19 (7, 43)	28 (13, 49)		0.193
Length of hospital stay, days	38.5 (21, 62.8)	42 (24, 73)		0.243
Cost, thousand CHY	189 (97–327)	202 (103–362)		0.469

OR denotes odds ratio, *CI* confidence intervals, *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury, *PCD* percutaneous catheter drainage, *NPI* negative pressure irrigation, *ED* endoscopic necrosectomy, *ACS* abdominal compartment syndrome, *ICU* intensive care unit

[a] One or more events in the same patient were considered as one end point

[b] Patients needed emergency surgery due to ongoing deteriorated organ functions or uncontrolled abdominal bleeding

[c] Patients with pre-existing diabetes needed higher dose of oral antidiabetic agent or insulin during or after the course of acute pancreatitis

[d] Patients with pre-existing coronary disease developed atrial fibrillation, stroke, heart failure ormyocardial infarction during or after the course of acute pancreatitis

[e] Symptoms of the patients with pre-existing chronic lung disease deteriorated during or after the course of acute pancreatitis

[f] Patients with pre-existing chronic renal insufficiency developed renal failure during or after the course of acute pancreatitis

Table 4 Subgroup analysis for the outcome of the patients underwent the two different approaches

Variable	Four-step group (n = 137)	Two-step group (n = 92)	OR (95% CI)	p value
Subgroups, no. (%)				0.052
Moderately severe	41 (29.9)	39 (42.4)	0.58 (0.33–1.01)	
Severe	96 (70.1)	53 (57.6)	1.72 (0.99–2.99)	
Hospital mortality, no. (%)				
Moderately severe	1 (2.4)	2 (5.1)	0.46 (0.04–5.32)	0.527
Severe	31 (32.3)	24 (45.3)	0.58 (0.29–1.15)	0.116
New-onset organ failure, no. (%)				
Moderately severe	3 (7.3)	6 (15.4)	0.43 (0.10–1.87)	0.254
Severe	19 (19.8)	22 (41.5)	0.35 (0.17–0.73)	0.004
New-onset intra-abdominal bleeding, no. (%)				
Moderately severe	2 (4.9)	5 (12.8)	0.35 (0.06–1.92)	0.209
Severe	22 (22.9)	29 (54.7)	0.25 (0.12–0.51)	<0.001
New-onset gastrointestinal fistula, no. (%)				
Moderately severe	2 (4.9)	8 (20.5)	0.20 (0.04–1.00)	0.035
Severe	22 (22.9)	21 (39.6)	0.45 (0.22–0.94)	0.031
Length of ICU stay, days				
Moderately severe	6 (2.5, 11.5)	19.5 (7.8, 33.8)		0.001
Severe	27 (14, 50)	36 (20.5, 54.5)		0.401
Length of hospital stay, days				
Moderately severe	22.5 (14.2, 41.8)	39 (21, 57.5)		0.013
Severe	46.5 (27, 73.2)	49 (30, 82.5)		0.630
Cost, thousand CHY				
Moderately severe	84 (51, 129)	117 (61, 205)		0.064
Severe	245 (147, 411)	290 (170, 431)		0.256

Patients were divided into three subgroups according to the presence of organ failure before intervention: (1) Severe AP: without organ failure; (2) Critical AP: with single or multiple organ failure

OR denotes odds ratio, *CI* confidence intervals, *ICU* intensive care unit

Stratified analysis

We then performed a stratified analysis to compare the incidence of mortality and major complications following the conventional and novel approach, respectively, in the subgroup patients with moderately severe AP or severe AP (Table 4). In patients with severe AP, no statistical difference was shown in the mortality rate between those treated with novel four-step approach and the conventional approach (31/137 vs. 24/92, OR for four-step approach: 0.58, 95% CI 0.29–1.15, $p = 0.116$). Similar results were also seen in the incidence of new-onset organ failure, intra-abdominal bleeding as well as gastrointestinal fistula. Nevertheless, in the patients with moderately severe AP, patients treated with the four-step approach had markedly shorter hospital and ICU stays and also a tendency toward less cost than those treated with the conventional approach, probably attributing to the less invasiveness of this novel step-up approach. Whereas, the differences were not statistically significant in terms of mortality, new-onset organ failure and intra-abdominal bleeding between the subgroup patients with moderately severe AP following the two different strategies.

Discussion

Since 2006 when the PANTER study came out [29], step-up approach has gradually become the mainstream for managing IPN. In this study, we compared our novel four-step approach, which combined three minimally invasive techniques, namely PCD, NPI and ED, and operation together with the conventional two-step strategy (PCD and open surgery). Although no significant difference was detected in overall mortality, the incidence of organ failure, local and systemic complications (e.g. intra-abdominal bleeding, fistula) decreased dramatically in patients receiving the four-step approach. With the aid of these minimally invasive techniques, about four fifths of the participants (109 of 137 patients, 79.6%) avoided open

Table 5 Detailed information about operation and postoperative complications in the patients underwent the two different approaches

Variable	Four-step group (n = 137)	Two-step group (n = 92)	OR (95% CI)	p value
Patients received operation, no. (%)	28/137	51/92	0.21 (0.12–0.37)	<0.001
Time interval between AP onset to operation, days	35.5 (27.8, 49.5)	29 (20, 39)		0.036
Reason for the primary operation, no. (%)				
Progression of septic shock	13 (46.4)	40 (78.4)	0.24 (0.09–0.65)	0.004
Uncontrolled intra-abdominal bleeding	12 (42.8)	9 (17.6)	3.50 (1.24–9.89)	0.015
Uncontrolled gastrointestinal fistula	3 (10.7)	1 (2.0)	6.00 (0.59–60.66)	0.090
Ongoing ACS	0 (0)	1 (2.0)	–	0.456
Postoperative complications, no. (%)				
New-onset organ failure	9 (32.1)	22 (43.1)	0.62 (0.24–1.64)	0.338
ARDS	2 (7.1)	5 (9.8)	0.71 (0.13–3.91)	0.691
AKI	3 (10.7)	5 (9.8)	1.10 (0.24–5.01)	0.898
Shock	7 (25.0)	16 (31.4)	0.73 (0.26–2.06)	0.551
Intra-abdominal bleeding	4 (14.3)	21 (41.2)	0.24 (0.07–0.79)	0.014
Gastrointestinal fistula	5 (17.8)	23 (45.1)	0.26 (0.09–0.81)	0.015
Gastric fistula	0 (0)	2 (3.9)	–	0.289
Intestinal fistula	2 (7.1)	6 (11.8)	0.58 (0.11–3.07)	0.515
Colonic fistula	3 (10.7)	15 (29.4)	0.29 (0.08–1.10)	0.058
Postoperative mortality, no. (%)	16 (57.1)	18 (35.3)	2.44 (0.95–6.28)	0.061
Postoperative length of hospital stay, days	10 (3.8, 31)	22 (7.8, 44.2)		0.106
Postoperative length of ICU stay, days	6.5 (2, 13.5)	11.5 (5, 22.8)		0.074

OR denotes odds ratio, *CI* confidence intervals, *ACS* abdominal compartment syndrome, *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury

surgery and most of them successfully survived with a mortality of 14.7%, suggesting that this novel four-step approach was a safe and efficient strategy.

Compared with our previous two-step approach, the most pivotal change we made in the novel four-step approach is the introduction of CNPI, which enables continuous irrigation of IPN and percutaneous endoscopic intervention. Different from PCD, CNPI is supposed to be an active drainage procedure, which could better drain the liquefied necrosis and reduce the incidence of sepsis and organ failure [30]. Besides, it is reported that continuous negative pressure could help decrease bacterial proliferation, accelerate the liquefaction of solid necrotic tissue and the formation of granulation tissue, therefore CNPI is probably helpful in walling off the necrotic tissue and controlling consequent local and systemic complications such as intra-abdominal bleeding, septic shock and gastrointestinal fistula. In the present study, with the addition of CNPI and ED, the four-step approach significantly lower the incidence of several lethal complications including MOF [12.5% (17/137) vs. 25.0% (23/92)], intra-abdominal bleeding [17.5% (24/137) vs. 37.0% (34/92)] as well as gastrointestinal fistula [17.5% (24/137) vs. 31.5% (29/92)]. Although CNPI is supposed to be a unique technique in our center, similar instrument had been described before by Raraty et al., and the results were also encouraging by showing fewer complications with minimally access approach [5, 31].

Another merit offered by CNPI is that the sinus tract it created could be used repeatedly to perform percutaneous endoscopic debridement and therefore limit the impairment of ED procedures to the most extent. The use of endoscope and laparoscope in the management of IPN had been reported frequently in the literature. Barton et al. [32] first used transmural endoscopic drainage (TED) in managing infected necrosis in SAP patients. However, TED was only applicable to those IPN patients whose necrotic tissue was adjacent to the stomach or duodenum. Bang et al. [14] introduced an endoscopic step-up approach combining endoscopic and percutaneous drainage together. Although it was practicable in most of IPN patients, it might be less effective in those patients with massive solid necrosis. Endoscopic necrosectomy was also proved to be effective in another study conducted by Liu et al. [33]; however, the detailed procedure for the endoscopic necrosectomy was not described in their study.

When it comes to the VARD, which was designed to debride the necrosis with the aid of nephroscope or laparoscope through the retroperitoneal route, previous studies had reported its value in treating IPN [12, 34]. However, due to the risk of inducing acute peritonitis, VARD could only be performed retroperitoneally. Differently, as our ED is implemented through the mature sinus tract 4–6 days after the CNPI procedure, both peritoneal and retroperitoneal route can be used safely as needed. Previous study also reported that endoscopic drainage through a mature sinus tract could avoid acute peritonitis [35]. In our study, ED was applied in 34 (24.8%) patients and the median number of EDs they received was 3 (IQR 2–4, range 1–7) times during the hospitalization, with a 3-day or 4-day interval. For all patients, no procedure-related complications were found including but not limited to peritonitis.

Results from the subgroup analysis revealed that severe patients profited more from the novel four-step approach in terms of incidence of new-onset organ failure, local and systemic complications, etc., probably because that the four-step approach was more aligned with the Damage Control Principal [36]. Besides, length of hospital and ICU stay was comparable in the two groups, indicating that, despite the more steps it contained, the novel four-step approach did not prolong and even tended to reduce the length of hospital stay. In patients with moderately severe AP, the length of hospital and ICU stay was markedly reduced, implying substantial economic and resource-saving benefits when apply this novel four-step approach, although there was no significant difference in the incidence of new-onset complications. All the results suggested that AP patients with more severe type of disease could benefit more from this novel four-step approach clinically.

Our treatment strategy also contained some limitations. First, as we used a snare to remove the necrosis with the aid of gastroscope, our ED can hardly debride the necrosis as efficiently as nephroscope and laparoscope although it is less invasive and safer. In addition, it was notable that the postoperative mortality in the IPN patients receiving four-step approach tended toward higher than those receiving two-step approach, probably owing to the strict indication for ON in the four-step strategy. This also reminded us the importance of exploring the optimal timing for operation in further prospective study. Moreover, although there is no evidence to support the routine use of prophylaxis antibiotic so far, we applied intravenous antibiotic prophylaxis commonly during the study period depending mostly on the treatment physician. There were debates regarding the use of prophylactic antibiotics in the past, and it is mentioned that the use of prophylactic antibiotics reduces infection rates in necrotizing pancreatitis in the 2002 IAP guidelines [37]. However, in the 2013 IAP guidelines, intravenous antibiotic prophylaxis is not recommended any more [38]. And in the 2013 ACG guidelines, the use of antibiotics in patients with sterile necrosis is also not recommended [39]. In the future prospective studies, a standard protocol for the use of antibiotics should be designed to avoid bias.

Conclusion

As compared to the conventional two-step approach, the novel four-step approach could significantly reduce the rate of new-onset major complications and the need of emergency operations among the patients with IPN, especially in those with more severe type of acute pancreatitis. These results indicate that this novel four-step approach consisting of PCD followed, if necessary, by NPI followed, if necessary, by ED followed, if necessary, by ON, is a feasible and promising treatment strategy for the patients with IPN.

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Compliance with ethical standards

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References

1. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA (2010) Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 139:813–820
2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS, Acute Pancreatitis Classification Working G (2013) Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 62:102–111
3. Tsiotos GG, Luque-de Leon E, Sarr MG (1998) Long-term outcome of necrotizing pancreatitis treated by necrosectomy. Br J Surg 85:1650–1653
4. Connor S, Alexakis N, Raraty MG, Ghaneh P, Evans J, Hughes M, Garvey CJ, Sutton R, Neoptolemos JP (2005) Early and late complications after pancreatic necrosectomy. Surgery 137:499–505
5. Rau B, Bothe A, Beger HG (2005) Surgical treatment of necrotizing pancreatitis by necrosectomy and closed lavage: changing patient characteristics and outcome in a 19-year, single-center series. Surgery 138:28–39
6. Howard TJ, Patel JB, Zyromski N, Sandrasegaran K, Yu J, Nakeeb A, Pitt HA, Lillemoe KD (2007) Declining morbidity and mortality rates in the surgical management of pancreatic necrosis. J Gastrointest Surg 11:43–49

7. Rodriguez JR, Razo AO, Targarona J, Thayer SP, Rattner DW, Warshaw AL, Fernandez-del Castillo C (2008) Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. Ann Surg 247:294–299
8. Tong Z, Li W, Yu W, Geng Y, Ke L, Nie Y, Sun J, Ni H, Wang X, Ye X, Li N, Li J (2012) Percutaneous catheter drainage for infective pancreatic necrosis: is it always the first choice for all patients? Pancreas 41:302–305
9. Quan ZF, Wang ZM, Li WQ, Li JS (2003) Use of endoscopic naso-pancreatic drainage in the treatment of severe acute pancreatitis. World J Gastroenterol 9:868–870
10. Gardener ML, Roberts K, Morris-Stiff G, Smith AM (2012) Percutaneous minimally invasive necrosectomy following endoscopic transgastric drainage in acute necrotising pancreatitis. BMJ Case Reports 2012
11. Binek J, Fretz C, Meyenberger C (2006) Endoscopic transgastric debridement and drainage for splenic necrosis following an acute episode in chronic alcoholic pancreatitis. Endoscopy 38:639–640
12. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, van Goor H, Schaapherder AF, van Eijck CH, Bollen TL, van Ramshorst B, Nieuwenhuijs VB, Timmer R, Lameris JS, Kruyt PM, Manusama ER, van der Harst E, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, van Leeuwen MS, Buskens E, Gooszen HG, Dutch Pancreatitis Study G (2010) A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 362:1491–1502
13. Zerem E, Imamovic G, Susic A, Haracic B (2011) Step-up approach to infected necrotising pancreatitis: a 20-year experience of percutaneous drainage in a single centre. Dig Liver Dis 43:478–483
14. Bang JY, Holt BA, Hawes RH, Hasan MK, Arnoletti JP, Christein JD, Wilcox CM, Varadarajulu S (2014) Outcomes after implementing a tailored endoscopic step-up approach to walled-off necrosis in acute pancreatitis. Br J Surg 101:1729–1738
15. van Brunschot S, van Grinsven J, Voermans RP, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SA, Bruno MJ, Cappendijk VC, Consten EC, Dejong CH, Dijkgraaf MG, van Eijck CH, Erkelens GW, van Goor H, Hadithi M, Haveman JW, Hofker SH, Jansen JJ, Lameris JS, van Lienden KP, Manusama ER, Meijssen MA, Mulder CJ, Nieuwenhuis VB, Poley JW, de Ridder RJ, Rosman C, Schaapherder AF, Scheepers JJ, Schoon EJ, Seerden T, Spanier BW, Straathof JW, Timmer R, Venneman NG, Vleggaar FP, Witteman BJ, Gooszen HG, van Santvoort HC, Fockens P, Dutch Pancreatitis Study G (2013) 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 13:161
16. Babu RY, Gupta R, Kang M, Bhasin DK, Rana SS, Singh R (2013) Predictors of surgery in patients with severe acute pancreatitis managed by the step-up approach. Ann Surg 257:737–750
17. Horvath K, Freeny P, Escallon J, Heagerty P, Comstock B, Glickerman DJ, Bulger E, Sinanan M, Langdale L, Kolokythas O, Andrews RT (2010) Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections: a multicenter, prospective, single-arm phase 2 study. Arch Surg 145:817–825
18. van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, Boermeester MA, van Goor H, Dejong CH, van Eijck CH, van Ramshorst B, Schaapherder AF, van der Harst E, Hofker S, Nieuwenhuijs VB, Brink MA, Kruyt PM, Manusama ER, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, Cuesta MA, Wahab PJ, Gooszen HG, Dutch Pancreatitis Study G (2011) A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 141:1254–1263
19. Bradley EL 3rd (1993) A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg 128:586–590
20. Dellinger EP, Forsmark CE, Layer P, Levy P, Maravi-Poma E, Petrov MS, Shimosegawa T, Siriwardena AK, Uomo G, Whitcomb DC, Windsor JA, Pancreatitis Across Nations Clinical R, Education A (2012) Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg 256:875–880
21. Banks PA, Freeman ML (2006) Practice guidelines in acute pancreatitis. Am J Gastroenterol 101:2379–2400
22. Muddana V, Whitcomb DC, Papachristou GI (2009) Current management and novel insights in acute pancreatitis. Expert Rev Gastroenterol Hepatol 3:435–444
23. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
24. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C, Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment S (2013) Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 39:1190–1206
25. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, van Goor H, Schaapherder AF, van Eijck CH, Bollen TL, van Ramshorst B, Nieuwenhuijs VB, Timmer R, Lameris JS, Kruyt PM, Manusama ER, van der Harst E, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, van Leeuwen MS, Buskens E, Gooszen HG (2010) A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 362:1491–1502
26. Babu BI, Genovese T, Mazzon E, Riccardi L, Paterniti I, Galuppo M, Crisafulli C, Siriwardena AK, Cuzzocrea S (2012) Recombinant human activated protein C (Xigris) attenuates murine cerulein-induced acute pancreatitis via regulation of nuclear factor kappaB and apoptotic pathways. Pancreas 41:619–628
27. Tong Z, Ke L, Li B, Li G, Zhou J, Shen X, Li W, Li N, Li J (2016) Negative pressure irrigation and endoscopic necrosectomy through man-made sinus tract in infected necrotizing pancreatitis: a technical report. BMC Surg 16:73
28. Balthazar EJ (2002) Acute pancreatitis: assessment of severity with clinical and CT evaluation. Radiology 223:603–613
29. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, Boermeester MA, Bollen TL, Buskens E, Dejong CH, van Eijck CH, van Goor H, Hofker SS, Lameris JS, van Leeuwen MS, Ploeg RJ, van Ramshorst B, Schaapherder AF, Cuesta MA, Consten EC, Gouma DJ, van der Harst E, Hesselink EJ, Houdijk LP, Karsten TM, van Laarhoven CJ, Pierie JP, Rosman C, Bilgen EJ, Timmer R, van der Tweel I, de Wit RJ, Witteman BJ, Gooszen HG, Dutch Acute Pancreatitis Study G (2006) Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute

necrotising pancreatitis (PANTER trial): design and rationale of a randomised controlled multicenter trial [ISRCTN13975868]. BMC Surg 6:6

30. Li X, Liu J, Liu Y, Hu X, Dong M, Wang H, Hu D (2015) Negative pressure wound therapy accelerates rats diabetic wound by promoting agenesis. Int J Clin Exp Med 8:3506–3513
31. Raraty MG, Halloran CM, Dodd S, Ghaneh P, Connor S, Evans J, Sutton R, Neoptolemos JP (2010) Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. Ann Surg 251:787–793
32. Baron TH, Thaggard WG, Morgan DE, Stanley RJ (1996) Endoscopic therapy for organized pancreatic necrosis. Gastroenterology 111:755–764
33. Liu WH, Ren LN, Chen T, Liu LY, Jiang JH, Wang T, Xu C, Yan HT, Zheng XB, Song FQ, Tang LJ (2014) Abdominal paracentesis drainage ahead of percutaneous catheter drainage benefits patients attacked by acute pancreatitis with fluid collections: a retrospective clinical cohort study. Crit Care Med 43(1):109–119
34. Logue JA, Carter CR (2015) Minimally invasive necrosectomy techniques in severe acute pancreatitis: role of percutaneous necrosectomy and video-assisted retroperitoneal debridement. Gastroenterol Res Pract 2015:693040
35. Rana SS, Bhasin DK (2005) Endoscopic therapy for organized pancreatic necrosis: are we as endoscopists organized? Trop Gastroenterol 26:173–177
36. Pommerening MJ, Kao LS, Sowards KJ, Wade CE, Holcomb JB, Cotton BA (2015) Primary skin closure after damage control laparotomy. Br J Surg 102:67–75
37. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, Carter R, Di Magno E, Banks PA, Whitcomb DC, Dervenis C, Ulrich CD, Satake K, Ghaneh P, Hartwig W, Werner J, McEntee G, Neoptolemos JP, Buchler MW, International Association of P (2002) IAP guidelines for the surgical management of acute pancreatitis. Pancreatology 2:565–573
38. Working Group IAPAPAAPG (2013) IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 13:e1–15
39. Tenner S, Baillie J, DeWitt J, Vege SS, American College of G (2013) American college of gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 108(1400–1415):1416