

Benefits of abdominal paracentesis drainage performed ahead of percutaneous catheter drainage as a modification of the step-up approach in acute pancreatitis with fluid collections

E. Zerem^{1,2}, S. Kunosić³, D. Zerem⁴, A. Boloban⁵, O. Zerem⁶, E. Zlomužica⁷

(1) Department of Medical Sciences, The Academy of Sciences and Arts of Bosnia and Herzegovina, Bistrik 7, 71000 Sarajevo, Bosnia and Herzegovina ; (2) Department of health sciences, „Džemal Bijedić“ University of Mostar, 88000 Mostar, Bosnia and Herzegovina ; (3) Department of Physics, Faculty of Natural Sciences and Mathematics, University of Tuzla, 75000 Tuzla, Bosnia and Herzegovina ; (4) Department of Internal Medicine, Cantonal Hospital „Safet Mujić“ Mostar, 88000 Mostar, Bosnia and Herzegovina ; (5) Department of Internal Medicine, Cantonal Hospital „Safet Mujić“ Mostar, 88000 Mostar, Bosnia and Herzegovina ; (6) Medical Faculty, University of Tuzla, 75000 Tuzla, Bosnia and Herzegovina ; (7) Department of health sciences, „Džemal Bijedić“ University of Mostar, 88000 Mostar, Bosnia and Herzegovina.

Abstract

Aim : The aim of the study is to evaluate the role of abdominal paracentesis drainage (APD) ahead of percutaneous catheter drainage (PCD), as a modification of the step-up approach, when treating acute pancreatitis (AP) with peritoneal ascitic fluid (PAF).

Patients and methods : This is a prospective cohort study including 118 participants with AP in which the indicative factors for upgrading from APD to PCD were investigated in patients with PAF. Ninety six patients with a sufficient volume of PAF initially underwent ultrasound-guided APD and were separated into two groups : group A (the patients who did not undergo PCD after APD) and B (the patients who underwent PCD after APD). Participants with AP who underwent PCD but lacked enough PAF for APD before PCD were followed up in a separate group (group C). Primary outcome was conversion rate to more aggressive procedure (percutaneous treatment modalities to surgery or death).

Results : Of the 96 patients who underwent APD, 42 were managed with APD alone and 54 received PCD after APD (14 required necrosectomy after initial PCD). APD led to a large decrease in levels of the initial severity scores and laboratory variables in both groups of patients with PAF. The reduction in levels of all evaluated predictive severity scores and laboratory variables was similar ($P>0.05$) after APD.

Conclusion : Application of APD ahead of PCD is safe and beneficial in the management of AP with abdominal or pelvic fluid collections. There are no relevant predictors that suggest whether APD is indicated or not. (*Acta gastroenterol. belg.*, 2020, 83, 285-293).

Key Words : acute pancreatitis, abdominal paracentesis drainage, percutaneous catheter drainage, the step-up approach, necrosectomy.

Introduction

Acute pancreatitis (AP), caused by impairment of the microcirculation of the pancreas during severe acute pancreatitis (SAP), can trigger massive pancreatic and peripancreatic necroses a very serious, life-threatening disease which can be associated with organ failure and local complications such as acute peripancreatic fluid collections (APFC), pancreatic necrosis, pseudocyst or abscess. APFC can occur in about 40% of patients early in the course of both mild and severe acute pancreatitis as enzyme-rich pancreatic juice collections. They resolve spontaneously in 50% of cases and intervention is usually not necessary (1-3). Therefore, some of the APFC can be treated conservatively, with follow-up and proper intravenous hydration. However, in some patients gross

destruction of the pancreatic gland can cause systemic release of numerous cytokines and inflammatory mediators, leading to activation of inflammatory cells, fever, and multiorgan failure (1-4). Besides, after the first 1-2 weeks from the onset of SAP, a transition from a pro-inflammatory to an anti-inflammatory response occurs. During this “second or late phase” of SAP, the patient is at risk of the translocation of intestinal flora due to intestinal barrier failure, which is followed by the development of secondary infection in the pancreatic or peripancreatic necrotic tissue and fluid collections (5,6).

The appropriate treatment of pancreatic necrosis, with liquefied debris and collections in the pancreatic and peripancreatic regions, with existence of abdominal or pelvic fluid, remains the subject of much debate. Recently, the step-up approach consisting of percutaneous catheter drainage (PCD) followed, if necessary, by (minimally invasive) necrosectomy, has been included in the management of SAP (7-9). However, if pancreatic necroses are associated with the peritoneal ascitic fluid this approach may not be optimal and may require further improvement.

Based on the revised Atlanta classification of AP (10), which differentiates among APFC, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis, some authors recommend a novel step-up approach whereby PCD is carried out after abdominal paracentesis drainage (APD) (11-14). APD may be justified in this clinical setting because the removal of toxic mediators and inflammatory substances from seroperitoneum may ameliorate the systemic consequences induced by SAP. In general, APD serves as a preparatory step for ensuing PCD with intention to achieve more effective results than those of the traditional step-up approach.

In this study, we present our experience and evaluate whether it is beneficial to perform APD ahead of PCD when treating AP patients with fluid collections.

Correspondence to : Enver Zerem, M.D., Ph.D., Department of health sciences, „Džemal Bijedić“ University of Mostar 88000 Mostar, Bosnia and Herzegovina. E-mail : zerem@live.com

Submission date : 31/12/2018

Acceptance date : 10/09/2019

Patients and methods

1. Design

This is a prospective cohort study in which we investigated the indicative factors for upgrading from APD to PCD in patients with moderately severe acute pancreatitis (MSAP) or SAP with peritoneal ascitic fluid. The study was performed at the university based tertiary Internal Medicine Hospital in Tuzla, Bosnia and Herzegovina between January 2011 and January 2018.

The patients with a sufficient volume of peritoneal ascitic fluid who had initially been treated by ultrasound-guided APD were divided into two groups: group A (the patients who did not undergo PCD after APD) and B (the patients who underwent PCD after APD). Participants with AP who underwent PCD yet lacked enough fluid collections in the abdominal or pelvic cavities for APD before PCD, were followed up in a separate group (group C).

This study was performed according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee at the University Clinical Center Tuzla. All patients included in the study gave written informed consent before participating.

Inclusion Criteria

Patients were enrolled if they had symptoms and signs of MSAP or SAP and if pancreatic or/and peripancreatic fluid collections were confirmed by ultrasound or computed tomography examination (CT) with one or more of the following (10): (1) fluid collections within two weeks of disease onset; (2) single or multi-organ failure; (3) initial computerized tomography severity index (CTSI) ≥ 7 ; and (4) acute physiology and chronic health evaluation (APACHE) II score > 8 .

Exclusion Criteria

The exclusion criteria were: (1) patients who underwent necrosectomy directly after APD without PCD as a bridge therapy; (2) previous surgical necrosectomy before APD during an episode of pancreatitis; (3) previous exploratory laparotomy for acute abdomen and intraoperative diagnosis of AP; (4) history of pancreatic carcinoma or chronic pancreatitis, (5) pregnancy and (6) inability of patients to cooperate.

2. Criteria for monitoring and clinical improvement

All patients were assessed clinically and monitored during daily rounds until they were discharged from the hospital or referred to surgery. Patients' response to treatment in terms of clinical symptoms and laboratory tests were monitored. The pancreatitis-specific clinical scores (Ranson, APACHE II, Marshall) were evaluated.

Age, etiology, length of hospital stay, C-reactive protein (CRP), S-amylase and lipase, hemogram, and coagulogram were also followed. Blood cultures were taken if a fever was present.

Initial contrast-enhanced CT was performed within the first week of the disease onset and repeated depending on the indication. A transabdominal ultrasound was performed where necessary. CTSI were calculated for each patient at the time of admission and serially calculated before and after each type of intervention.

Severity was determined primarily according to (a) the Atlanta criteria including the presence of local and systemic complications, and according to pancreatitis-specific clinical, radiological and laboratory findings taken on admission to the hospital (10). According to Ranson score, 0–2 characterizes mild AP and 3 or more severe AP. According to APACHE II score, 0–8 characterizes mild AP and 9 or more severe AP. The levels of CRP higher than 150 mg/L were considered indicative of severe inflammation.

Clinical improvement was defined as improved function of at least two organ systems (i.e., circulatory, pulmonary, or renal), or improvement of 2 out of 3 parameters of infection (i.e., C-reactive protein, leucocytes, or temperature) according to the criteria from PANTER trial (7). Each step was evaluated 72 hours after intervention and considered successful in cases of clinical improvement. Clinical failure was defined as the absence of clinical improvement or as clinical deterioration.

3. Outcome measures

Primary outcome was conversion rate to more aggressive procedure (percutaneous treatment modalities to surgery or death). Secondary outcomes were catheter dwell time, catheter changes per patient, number of interventions required, reduction of abdominal or pelvic collections after APD, improvement of the relevant severity scores and laboratory parameters of AP after APD, length of intensive care unit (ICU) and hospital stay.

4. Indications for interventions

4.1 Indication for APD

APD management was introduced to AP patients with a sufficient volume of abdominal or pelvic fluid collections (more than 50 ml) and a feasible pathway for image-guided APD.

4.2 Indications for PCD.

Percutaneous drainage of pancreatic and peripancreatic fluid collections under ultrasonographic guidance was performed in cases where intensive conservative treatment alone (group C) and APD (group B) could not improve the patients' condition (Figure 1). The

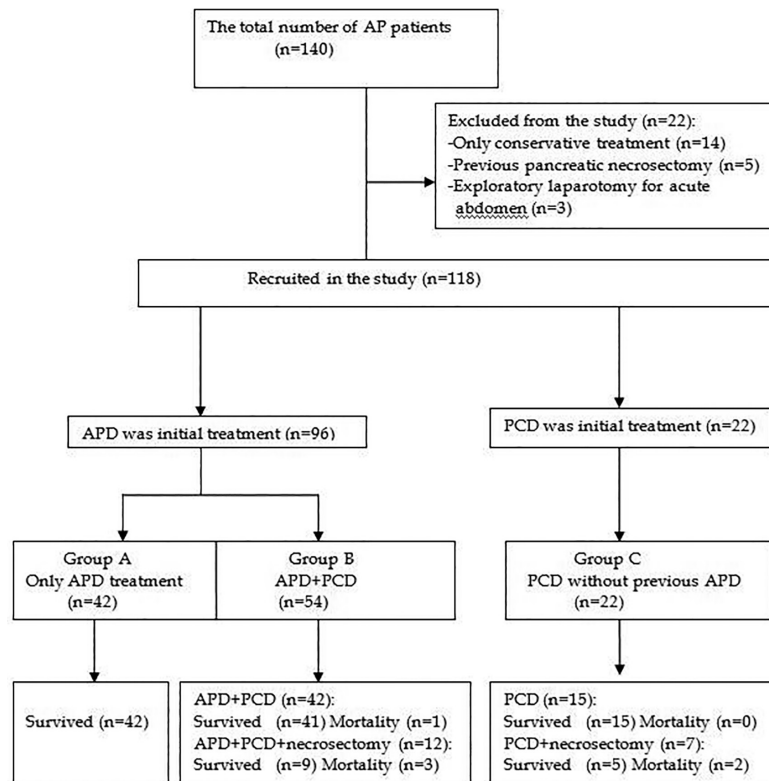


Figure 1. — The flow chart of research work : it describes the process of enrolling qualified patients, and introduces the protocol of step-up strategy in managing AP patients.

decision to convert to PCD was made by the experienced physician and was based on ongoing fevers and other clinical evidence of sepsis according to the consensus of AP treating board in our institution.

4.3. Indications for necrosectomy

Surgical treatment was planned only when the results of the previous medical treatment, including APD and PCD, revealed no clinical improvement (persistent fever, persistently raised or increasing trend of white blood cell (WBC) count, worsening or new-onset of organ failure, inadequate drainage of collections and necrosis, and presence of ongoing necrosis with bowel complications). Inadequate drainage of collections and necrosis is defined as persistence of necrosis and residual fluid collections despite repeated repositioning and flushing of the catheter and additional catheter placements.

5. Minimally invasive step-up treatment strategy

5.1 Conservative management

All patients included in the study received standard intensive care treatment. It consisted of supportive care including maintenance of circulation volume to prevent electrolyte imbalance, nutritional supplements, analgesics, oxygen supplementation, mechanical ventilation, as well as monitoring for respiratory, cardio-

vascular and renal insufficiencies and correcting them early. Enteral nutrition was introduced in the early phase of AP unless paralytic ileus was presented (8,15).

5.2. Percutaneous drainage procedures

APD and PCD interventions were applied according to indications and performed under ultrasound guidance. APD can be described as percutaneous puncture and catheterization of peritoneal ascitic fluid. In cases where APD could not improve the patients' condition as the third step in the step-up approach of management protocol, PCD was applied to eliminate the liquefied debris and collections in the peripancreatic regions. The applied drainage technique was the trocar method that is described in more details in earlier studies (7,8,12).

6. Statistical analysis

Statistical analysis was done using statistical software SPSS 20.0. Kolmogorov-Smirnov tests of normality were applied to check the normality of data. If the data were normally distributed, the means were compared using Student's t test between two groups, and for skewed data, the Mann-Whitney test was applied. Categorical data were expressed as counts and proportions ; continuous data were expressed as means and standard deviations. Proportions were compared using the Chi-squared test or Fisher exact test, whichever was applicable. A value of $P < 0.05$ was considered as indicative of significance.

Results

There were 140 patients with AP who were admitted to our hospital during the study period. All patients were admitted within 24 hours of the onset of symptoms. Participants enrolment process is summarized in Figure 1. Twenty two patients were excluded thereby leaving a total of 118 patients included in the study. Of the 118 patients enrolled in the study, 96 were managed with APD as an initial treatment (42 patients were treated with APD alone (Group A) and 54 received PCD after initial APD (Group B)) and 22 patients (without a sufficient volume of abdominal or pelvic fluid but with liquefied debris and collections in the peripancreatic regions) were managed without APD before PCD (Group C). A total of 98 patients were successfully treated without needing

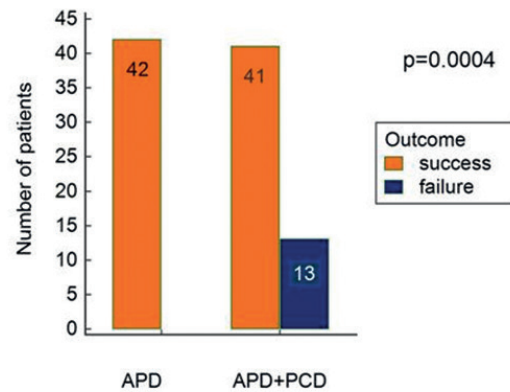


Figure 2. — The association between treatment modalities and the patients' outcomes. APD- abdominal paracentesis drainage, PCD- percutaneous catheter drainage.

Table 1. — The characteristics of 118 patients with acute pancreatitis treated by APD-alone (Group A), PCD after APD (Group B) and by PCD-alone (Group C)

Characteristics	Group A (N=42)	Group B (N=54)	P value	Group C (N=22)
Demographic data				
Age, years, \pm SD	52.14 \pm 14.12	50.96 \pm 10.62	0.93	50.23 \pm 13.21
Sex, male/female	26/16	32/22	0.93	14/8
Etiology of acute pancreatitis, n				
-alcohol related	19	27	0.884	11
-gallstones	10	13	0.950	6
-hypertriglyceridaemia	5	4	0.561	1
-trauma	2	3	0.977	1
-other	6	7	0.982	3
Atlanta classification severity, n				
moderately-severe/severe	24/18	22/32	0.234	9/13
Severity scores				
Acute Ranson Score, \pm SD	2.76 \pm 1.5	3.56 \pm 2	0.147	3.5 \pm 2
Initial APACHE II score, \pm SD	12.4 \pm 7.4	17.7 \pm 11	0.067	16.3 \pm 11.3
Initial Marshall score, \pm SD	3.07 \pm 1.44	4.22 \pm 1.33	0.012	3.86 \pm 1.46
SIRS, n(%)	24(57.1)	34(62.9)	0.746	12(54.5)
Organ failure, n(%)	29(69)	44(81.5)	0.362	17(77.3)
-multiple-organ failure,	9(21.4)	25(46.3)	0.041	8(36.4)
-organ failure lasts: < 48 h/>48h	11/18	12/32	0.45/0.18	8/9
Duration of organ failure, days	15.66 \pm 15.18	23.43 \pm 18.00	0.239	24.59 \pm 22.80
Initial CRP, mg/L, \pm SD	128.4 \pm 102.1	159.6 \pm 129.6	0.619	152.2 \pm 139.3
Initial WBC count ($\times 10^9/L$)	11.8 \pm 3.8	14.9 \pm 5.5	0.018	13.4 \pm 3.9
Initial S-amylase level, U/l	937.2 \pm 497.5	935.5 \pm 511.5	0.981	922.8 \pm 384.9
Initial S-lipase level, U/l	1113.7 \pm 469.0	1189.6 \pm 587.5	0.340	1162.8 \pm 45.1
CTSI, mean \pm SD	5.9 \pm 1.6	7.9 \pm 1.9	<0.001	7.6 \pm 2.2
Extent of necrosis, n (%)				
Less than 30%	12(29.6)	8(14.8)	0.250	4(18.2)
30-50%	24(57.1)	25(46.3)	0.513	10(45.5)
More than 50%	6(14.3)	21(38.9)	0.024	8(36.4)
Incidence of infections, n(%)				
Polymicrobial infections	28(66.7)	41(75.9)	0.460	14(63.6)
Monomicrobial infections	7(16.7)	7(12.9)	0.807	4(18.2)
No infection	7(16.7)	6(11.2)	0.636	4(18.2)
The incidence of bacteraemia, n (%)	14(33.3)	23(42.6)	0.640	9(40.9)
Hospital stay, days	30.5 \pm 18.4	57.7 \pm 19.1	<0.001	60.3 \pm 24.4
Days in intensive care unit	4.5 \pm 6.7	7.9 \pm 7.3	0.019	9.0 \pm 8.1

APD : abdominal paracentesis drainage ; PCD : percutaneous catheter drainage ; CTSI : computerized tomography severity index ; \pm SD : mean; n-number of patients ; h : hours ; AP : acute pancreatitis ; CRP : C-reaction protein ; WBC : white blood cell.

Table 2. — The detailed information of APD interventions, laboratory and clinical parameters after APD between patients treated by APD-alone (Group A) and PCD after APD (Group B)

Characteristics	Group A (N=42)	Group B (N=54)	P
<i>Details for APD intervention</i>			
AP onset to first APD, days \pm SD	10.45 \pm 3.9	11.56 \pm 3.7	0.701
Number of APD catheters per patient			0.380
Mean \pm SD	1.6 \pm 0.83	1.8 \pm 0.93	
Median (range)	1 (1-3)	2 (1-4)	
APD catheter duration, days			0.001
Mean \pm SD	15.2 \pm 9.46	22.1 \pm 9.57	
Median (range)	11 (4-38)	21 (7-45)	
Total APD procedures per patient			
Mean \pm SD	3.1 \pm 2.29	3.9 \pm 1.98	0.06
Median (range)	2 (1-7)	4 (1-8)	
<i>Volume of liquid aspirated after APD, n(%)</i>			0.083
50-150 ml	7(16.6)	8(14.8)	0.8
150-300 ml	28(66.7)	26(48.1)	0.07
More than 300 ml	7(16.6)	20(37.1)	0.03
Reduction of abdominal fluid, %(range)	82.57(55-100)	30.37(10-60)	<0.001
Reduction of PFC by <50% after APD, n,%	0(0)	41(75.9)	<0.001
<i>Severity scores after APD</i>			
APACHE II score, \pm SD	7.1 \pm 3.78	11.9 \pm 11.1	0.009
Ranson score, \pm SD	2.1 \pm 0.96	2.9 \pm 2.1	0.014
Marshall score, \pm SD	1.9 \pm 0.85	3.1 \pm 1.66	<0.001
CRP after APD, mg/L, \pm SD	70.3 \pm 57.1	121 \pm 116.6	0.011
The recovery of WBC, days, \pm SD	22.5 \pm 8.97	29.9 \pm 16.42	0.024
Time for sepsis reversal, days, \pm SD	14.7 \pm 4.41	22.6 \pm 5.65	<0.001
Organ failure reversal after APD, n(%)	15/29(51.7)	17/44(38.6)	0.7/0.16
<i>Amilase and lipase level in APD aspirated fluid</i>			
Amylase level in aspirated fluid, U/l, \pm SD	245.4 \pm 436	636.7 \pm 877	0.01
N of patients with amylase >1 \times 10 ³ U/L, n,(%)	5(11.9)	13(24.1)	0.13
Lipase level in aspirated fluid, U/l \pm SD	471.1 \pm 654	792.9 \pm 1031	0.08
N of patients with lipase >1.5 \times 10 ³ U/L, (%)	6(14.3)	14(25.9)	0.16

APD : abdominal paracentesis drainage ; PCD : percutaneous catheter drainage ; \pm SD : mean \pm SD ; n : number of patients ; h : hours ; d : days ; AP : acute pancreatitis ; CRP : C-reaction protein ; AP : onset to first APD-interval between the onset of symptoms and first APD insertion ; AF : aspirated fluid after APD ; PFC : (per)pancreatic fluid collection.

necrosectomy (42 in APD-alone group, 41 in the APD + PCD group and 15 in the PCD-alone group). One patient from APD+PCD group died during treatment due to a massive gastrointestinal bleeding, whereas the remaining 19 patients (12 in the APD + PCD group and 7 in the PCD-alone group) required necrosectomy after the drainage interventions (Figure 2).

The demographic characteristics, clinical, radiological and laboratory data of 118 patients recruited in the study are shown in Table 1. Alcohol and biliary calculus were the causes of AP in over 70% of the cases. The demographic data (age, sex, and etiology) were comparable between groups ($P > 0.05$).

The parameters for assessing the severity of the clinical course of acute pancreatitis are presented in Table 1. The APACHE II and Ranson scores, the incidence of sepsis, initial values of CRP, serum amylase and lipase levels were not significantly different between groups. Initial WBC count, Marshall score, number of failed organs, CTSI, intensive care unit length, and hospital stay were significantly higher in the APD + PCD group compared to the APD group ($P < 0.05$), but were similar

to those of the PCD-alone group ($P > 0.05$) (Table 1). Having compared the relevant parameters for assessing the severity of the clinical course of acute pancreatitis, that are suitable for statistical evaluation of their direct association with APD in both groups (A and B) our results have shown that APD led to a large decrease in those severity scores and laboratory parameters in both groups (A and B) (Table 1, Table 2). However, there was no statistically significant difference in the reduction of levels of all severity scores and laboratory parameters which are evaluated since all evaluated parameters had similar reduction values ($P > 0.05$) after APD.

The parameters for assessing the severity of the clinical course of acute pancreatitis such as initial WBC count, Marshall score, number of failed organs, CTSI were similar in the APD + PCD group compared to the PCD-alone group ($P > 0.05$) (Table 1, Table 3).

The duration of PCD was significantly higher in the PCD-alone group compared with the APD + PCD group ($P < 0.05$). The number of catheters per patient, used under PCD, was significantly higher in the PCD-alone group (40 in 22 patients) than in the APD + PCD

Table 3. — Details for PCD intervention, laboratory and clinical parameters between patients treated by PCD after APD (Group B) and PCD-alone (Group C)

Characteristics	Group B (N=54)	Group C (N=22)	P
Details for APD intervention			
APD onset to first PCD, days ± SD	27.1 ± 5.29	22.1 ± 3.15	<0.001
Number of PCD catheters per patient			
Mean ± SD	1.38 ± 0.74	1.82 ± 1.0	0.043
Median (range)	1 (1–4)	1 (1–4)	
PCD catheter duration (days)			
Mean ± SD	29.7 ± 9.8	37.8 ± 22.9	0.033
Median (range)	28.5 (9–65)	34.5 (13–82)	
Total PCD procedures per patient			
Mean ± SD	4.9 ± 2.38	6.1 ± 2.69	0.080
Median (range)	5 (1–10)	6 (1–11)	
Lipase and amylase level in PCD aspirated fluid			
Lipase level, U/l, ± SD	13023± 37106	8369± 13190	0.569
N of patients with lipase >1.5×10 ³ U/L,(%)	20(37)	11(50)	0.297
Amylase level in aspirated fluid, U/l	16209 ± 51119	11097± 20976	0.652
N of patients with amylase>1×10 ³ U/L,(%)	26(48.1)	11(50)	0.884

APD : abdominal paracentesis drainage ; PCD : percutaneous catheter drainage ; IQR : median, (interquartile range) ; ± SD : mean ± SD ; n : number of patients ; AP : acute pancreatitis ; AP : onset to first PCD-interval between the onset of symptoms and first PCD insertion.

Table 4. — The comparison of related parameters between drainage (APD and PCD) success and failure groups

Treatment method and severity of acute pancreatitis	Outcome of initial treatment, n (%)± SD		P value
	Success	Failure	
Treatment method, n(%) :			
APD only	42/42 (100)	0 (0)	<0.001
APD+PCD	41/54 (75.9)	13/54 (24.1)	<0.001
PCD only	16/22 (72.7)	6/22 (27.3)	0.004
APD overall	83/96(86.5)	13/96(13.5)	<0.001
Severity of pancreatitis:			
Initial APACHE II score, ≥9, n(%)	70/98(71.4)	20/20(100)	0.007
Initial APACHE II score, ± SD	12.79 ± 7.12	29.95 ± 11.6	<0.001
Initial Ranson score≥5, n(%)	22/98(22.5)	18/20(90)	<0.001
Initial Ranson, mean± SD	2.8 ± 1.59	5.68 ± 1.42	<0.001
Initial Marshall score≥3, n(%)	71/98 (72.4)	20/20(100)	0.009
Initial Marshall score, mean± SD	3.4 ± 1.34	5.47 ± 0.77	<0.001
Initial CTSI≥7, n(%)	52/98 (53)	19/20 (95)	0.001
Initial CTSI, ± SD	6.7 ± 1.94	9.63 ± 0.96	<0.001
Initial CRP, >150 mg/L, n(%)	49/98(50)	18/20 (90)	0.001
Initial CRP, mg/L, ± SD	119.3 ± 104.6	292.0 ± 106.5	<0.001
CRP after APD, mg/L, ± SD	69.4 ± 61.44	287.6 ± 76.73	<0.001
Initial S-amylase level, U/l	955.6± 502.8	820.1± 338.5	0.263
Initial S-lipase level, U/l, ± SD	1166.8± 521.1	1109.3± 392.3	0.649
Extent of necrosis over 50%,n(%)	17/98(17.3)	18/20(90)	<0.001
The incidence of sepsis	26/100(26)	20/20(100)	<0.001
APD catheter duration, days,± SD	17.07 ± 8.82	31.69 ± 8.52	<0.001
PCD catheter duration, days,± SD	28.16 ± 11.87	43.74 ± 17.98	<0.001
Amylase and lipase level in APD and PCD aspirated fluid			
Amylase in APD>1000 U/l, n(%)	13/84(15.5)	5/12 (41.7)	0.032
Amylase in PCD>1000 U/l, n(%)	20/58(34.5)	17/18(94.4)	<0.001
Lipase in APD>1500 U/L, n(%)	10/84(11.9)	10/12(83.3)	<0.001
Lipase in PCD>1500 U/L, n(%)	13/57(22.4)	18/19(94.7)	<0.001
Disease-specific mortality,n(%)	0/118	6/118(5.1)	0.014
Days in hospital, ± SD	42.43 ± 20.3	80.16 ± 14.42	<0.001
Days in intensive care unit, ± SD	5.16 ± 6.5	15.79 ± 5.09	<0.001

APD : abdominal paracentesis drainage ; PCD : percutaneous catheter drainage ; CTSI : computerized tomography severity index ; ± SD : mean ± SD ; n : number of patients ; AP : acute pancreatitis ; CRP : C-reactive protein.

group (75 in 54 patients) (P<0.05) (Table 3). The total number of interventional procedures (repositioning, replacements, flushing, and additional catheter placement under image guidance) was 403 (269 in 54 patients from

the APD+PCD group, and 134 in 22 patients from the APD-alone group) (P=0.08) (Table 3).

The total number of catheters used under APD in 96 patients was 166 (99 in 54 patients from the APD +

PCD group and 67 in 42 patients from the APD-alone group ($P>0.05$) (Table 2). Duration of APD and number of patients with amount of aspirated fluid more than 300 ml were significantly higher in the APD+PCD group compared with the APD-alone group. In contrast, the percentage of reduction of abdominal fluid after APD was significantly higher in the APD-alone group compared with the APD + PCD group ($P<0.05$) (Table 2).

Microbiological examination was done on blood samples of patients as well as on samples from contents obtained during APD and PCD. Among 101 out of 118 (86%) culture-positive patients, only 1 kind of offending organism was found in 18 patients, 2 organisms in 71 patients, and 3 species were identified in 12 patients. The microorganisms of positive cultures were predominantly gram negative, with *Escherichia coli* as the leading pathogen. Positive hemocultures was confirmed in 46 out of 118 (39%) patients. Positive hemocultures were always associated with polymicrobial infections in the contents obtained during APD (14 patients in group A) and/or the contents obtained during PCD (23 patients in B and 9 patients in C group) (Table 1). Microbiological infections of the contents obtained during PCD (group B) were always associated with positive cultures in the content of APD in those patients. WBC count recovery and the time for sepsis reversal after APD took longer in the patients in the APD+PCD group than in the APD-alone group ($P<0.05$) (Table 2).

Serum lipase and amylase level was similar in all three groups (Table 1). However, 18 patients had increased level of amylase (between 1049 and 3760 U/L; normal value: 25-125) and 20 patients increased level of lipase (between 1562 and 3427; normal value: 73-393 U/L) in APD aspirated fluid. Also, 37 patients (48.5%) had increased level of amylase (between 1394 and 351450 U/L) and 31 patients increased level of lipase (between 1687 and 234800 U/L) in PCD aspirated fluid (Table 2 and 3). Moreover, the number of patients with high levels of amylase and lipase in aspirated fluid obtained after APD and PCD was significantly higher in the failure group in comparison to the success group ($P<0.05$) (Table 4). Besides, 5/6 mortality patients had amylase and lipase level in PCD aspirated fluid more than 14267 U/L and 11763 U/L respectively.

The comparison of related parameters between initial method success and failure groups is presented in table 4. The success group included patients with clinical improvements after drainage (APD and PCD), and the failure group referred to those without clinical improvements after drainage treatments (e.g., those who received further necrosectomy, or died). The severity scores, incidence of sepsis, extent of necrosis over 50% and laboratory parameters (except the amylase and lipase serum levels), were significantly higher in the failure group in comparison to the success group ($P<0.05$). Also, the duration of APD and PCD, the ICU and hospital stay was significantly longer in the failure group compared to those of success group ($P<0.05$) (Table 4).

Of the 6 patients (5.1%) who died of the disease-specific mortality, 3 suffered from ongoing sepsis with multisystem organ failure (MOF), 2 developed MOF together with persistent/worsening sepsis and one patient died of massive gastrointestinal bleeding during PCD treatment. All 6 deceased had APACHE II score over 14, CTSI over 7, acute Ranson score over 5, and MOF.

Discussion

In our study, we aimed to determine whether application of APD ahead of PCD was safe and beneficial in the management of AP with abdominal or pelvic fluid collections. Considering that the 96 patients who underwent APD as the initial treatment, represented a seriously ill subset of patients, the successful outcome in 86.5% patients, the mortality of 4.2% and the proportion of patients requiring surgery of 12.5% are acceptable outcomes ($p=0.0004$) (Fig. 1 and 2). All patients with fatal outcome were in poor condition when admitted to our hospital, with high clinical scores for SAP, generalised retroperitoneal inflammation and MOF. Our results are comparable to the results of similar studies reported earlier on APD treated patients(11-14,16-19) thereby confirming that, the step-up approach in conjunction with APD, is a safe and effective treatment method for AP.

Management of AP ranges from supportive care with intravenous fluids for mild cases, to retroperitoneal necrosectomy for SAP. As it stands today, the step-up approach that can be summarized as: delayed intervention with close monitoring and conservative treatment, percutaneous or endoscopic catheter drainage and minimally invasive drain-guided debridement, may be considered the reference standard intervention for SAP (8,9,16-19). The severity of pancreatitis in our series, assessed by the clinical and radiological scores, was similar to other studies (11,12,20-23).

In our study, we performed image-guided percutaneous catheter drainage as an important step of the minimal invasive step-up approach. Percutaneous and endoscopic catheter drainage are two different methods that have important role in the step-up approach treatment of AP. Both methods have their advantages and disadvantages. The major advantage of endoscopic approach is that it creates a permanent pancreatico-gastric track, with no spillage of pancreatic enzymes out of digestive system in contrast to PCD, thereby reducing the risk of formation of pancreatico-cutaneous fistulas. However, in the case of infective complications or other drainage problems the monitoring, catheter manipulation and the analysis of the drainage content are very difficult or impossible with endoscopic, unlike with PCD approach.

Within the past few years, some authors (11-14,16) have advocated the concept of removing the peritoneal fluid found in AP which might reduce inflammation and disease severity since the intra-abdominal fluid accumulated during AP may contain factors that trigger and increase the severity of the disease, including

proinflammatory mediators and infection. Combining APD with PCD eliminates fluid collections leading to a more complete step-up approach by adding APD as the second step between conservative therapy and PCD.

The important question is, whether APD should become routine or whether there are predictors that tell us that we should opt for PCD or endoscopic drainage straight away. In our study, we observed the variables regarding subsequent interventions after APD and evaluated them in terms of subsequent PCD. Our results have shown that APD led to a large decrease in those severity scores and laboratory parameters in both groups (A and B) (Table 1 and 2). These results indicated that a large number of inflammatory factors were eliminated through drainage of the seroperitoneum by APD in both groups. Since the reduction in levels of all evaluated predictive severity scores and laboratory variables was similar ($P > 0.05$) after APD, we concluded that there are no predictive factors according to which it is possible to estimate whether APD is indicated for application or not (Figure 3). Since, the parameters for assessing the severity of the clinical course of AP were similar in the APD + PCD group compared to the PCD-alone group ($P > 0.05$) (Table 1, Table 3) we compared some variables such as hospital stay, days in intensive care unit (Table 1), number of PCD catheters per patient, PCD catheter duration, and total PCD procedures per patient (Table 3) between groups (B and C) with the intention to check if it is possible that APD prolonged hospital stay and increases the number of necessary drainage and catheters. According to our results, when PCD was preceded by APD, these patients did better than the PCD-alone group patients (Table 3), showing that the duration of PCD, number of interventional procedures, procedure related complications, hospital stay, and days in intensive care unit were higher in the PCD-alone group compared with the APD + PCD group (Table 1 and Table 3). In view of the above, it is evident that integrating APD into the step-up approach is beneficial for patients.

However, some studies report that prolonged peritoneal lavage can cause a large increase in late infections offsetting the benefit of APD due to the possible secondary infection of fluid collections which is the leading cause of mortality in patients with AP(24-26). Other authors report that APD did not increase the infectious complications and infection-related mortality compared with the strategy without APD in patients with AP(11-14,16). Our results regarding incidence of infection and sepsis, time for sepsis reversal and the recovery of WBC are comparable and similar to Liw et al. (11) study and support the statement that the fear of secondary infection during APD is excessive.

It is true that APD and PCD (especially if catheter remains for a long time) often lead to colonization of the cavity with microorganisms and results in superinfection. However, during the "second or late phase" of SAP, patient is at risk of the translocation of intestinal flora due to intestinal barrier failure, followed by the development

of secondary infection in the pancreatic or peripancreatic necrotic tissue and fluid collections, resulting in sepsis and late mortality. Thus, the patients with SAP are at risk of infection regardless of APD. Even more, in case of damage of the intestinal mucosal barrier and bacterial spread from large intestine to abdominal cavity with subsequent hematogenous spread, the analysis of infected content is impossible. However, in case of superinfection during PCD or APD the obtained content can be analysed in order to confirm the strain of microorganisms and prescribe appropriate antibiotics (5,8,27).

Some authors consider that digestive enzymes found in the abdominal fluid in AP are largely inactive and likely contribute minimally to the clinical course of AP (10,27, 28). In our study, serum lipase and amylase levels were similar in all three groups (Table 1) with no significant difference between serum lipase and amylase levels in the drainage method success and failure groups (Table 4).

However, several patients had increased levels of amylase and lipase in APD aspirated fluid, and even more patients had increased enzyme levels in PCD aspirated fluid. Moreover, the number of patients with high levels of amylase and lipase in aspirated fluid obtained after APD and PCD were significantly higher in the failure group in comparison to the success group ($P < 0.05$) (Table 4). In view of the above, the level of serum amylase and lipase cannot reflect the severity of AP. However, we think that the relationship between the level of pancreatic enzymes in abdominal fluid collection (especially in peripancreatic fluid collections, with extremely high values of pancreatic enzymes) and the severity of acute pancreatitis has still not been fully clarified.

Although, our study population is comparable with the subset and outcomes of previously reported studies about application of APD ahead of PCD, there are certain limitations to this conclusion due to the difference in clinical characteristics and the severity of enrolled patients which are, to a certain extent, incomparable amongst the studies. Also, the study reported the step-up strategy in treating AP, with introduction of APD as the second step, in a novel modified step-up approach without adequate experience and established technique. Different schemes of conservative management (antibiotic prophylaxis, supportive measures) have been used over the years, being one of the limitations.

We conclude that the step-up approach incorporating APD ahead of PCD, as the second step in the management of AP patients with peritoneal ascitic fluid, is safe and beneficial to patients since it reduces inflammatory factors, postpones further interventions, and delays or avoids multiple organ failure. In addition, APD does not increase the infectious complications and infection-related mortality compared with the strategy without APD in patients with AP. Therefore, according to our opinion, application of APD ahead of PCD, in the management of AP with abdominal or pelvic fluid collections, should be considered a routine procedure. Besides, the relationship between the levels of pancreatic enzymes in abdominal

fluid collections and clinical course of SAP has still not been fully clarified. Therefore, further larger-scale studies are needed to provide definitive answer regarding the relationship between the levels of pancreatic enzymes in abdominal fluid collections and clinical course of SAP.

Conflict of interest, disclosure and funding declaration

All authors : no conflict.

References

1. WALSER EM, NEALON WH, MARROQUIN S, RAZA S, HERNANDEZ JA, VASEK J. Sterile fluid collections in acute pancreatitis : catheter drainage versus simple aspiration. *Cardiovasc. Intervent. Radiol.*, 2006, **29** : 102-107.
2. BEGER HG, RAU BM. Severe acute pancreatitis : Clinical course and management. *World J. Gastroenterol.*, 2007, **13** : 5043-51.
3. ZEREM E, IMAMOVIĆ G, LATIĆ F, MAVIJA Z. Prognostic value of acute fluid collections diagnosed by ultrasound in the early assessment of severity of acute pancreatitis. *J. Clin. Ultrasound.*, 2013, **41** : 203-9.
4. VAN BAAL MC, VAN SANTVOORT HC, BOLLEN TL, BAKKER OJ, BESSELINK MG, GOOSZEN HG, Dutch Pancreatitis Study Group. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *Br. J. Surg.*, 2011, **98** : 18-27.
5. ZEREM E. Treatment of severe acute pancreatitis and its complications. *World J. Gastroenterol.*, 2014, **20** : 13879-92.
6. FREEMAN ML, WERNER J, VAN SANTVOORT HC, *et al.* Interventions for necrotizing pancreatitis : summary of a multidisciplinary consensus conference. International Multidisciplinary Panel of Speakers and Moderators. *Pancreas*, 2012, **41** : 1176-94.
7. VAN SANTVOORT HC, BESSELINK MG, BAKKER OJ, *et al.*, Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N. Engl. J. Med.*, 2010, **362** : 1491-502.
8. ZEREM E, IMAMOVIĆ G, SUŠIĆ A, HARAČIĆ B. Step-up approach to infected necrotising pancreatitis : a 20-year experience of percutaneous drainage in a single centre. *Dig. Liver Dis.*, 2011, **43** : 478-83.
9. BESSELINK MG. The 'step-up approach' to infected necrotizing pancreatitis : Delay, drain, debride. *Dig. Liver Dis.*, 2011, **43** : 421-2.
10. BANKS PA, BOLLEN TL, DERVENIS C, *et al.*, Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012 : revision of the Atlanta classification and definitions by international consensus. *Gut*, 2013, **62** : 102-11.
11. LIU WH, WANG T, YAN HT, *et al.* Predictors of percutaneous catheter drainage (PCD) after abdominal paracentesis drainage (APD) in patients with moderately severe or severe acute pancreatitis along with fluid collections. *PLoS One*, 2015, **10** : e0115348.
12. LIU WH, REN LN, CHEN T, *et al.* 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.*, 2015, **43** : 109-19.
13. WANG T, LIU LY, LUO H, *et al.* Intra-Abdominal Pressure Reduction After Percutaneous Catheter Drainage Is a Protective Factor for Severe Pancreatitis Patients With Sterile Fluid Collections. *Pancreas*, 2016, **45** : 127-33.
14. LIU L, YAN H, LIU W, *et al.* Abdominal Paracentesis Drainage Does Not Increase Infection in Severe Acute Pancreatitis : a Prospective Study. *J. Clin. Gastroenterol.*, 2015, **49** : 757-63.
15. MEIER R, OCKENGA J, PERTKIEWICZ M, PAPA, MILINIC N, MACFIE J, DGEM (GERMAN SOCIETY FOR NUTRITIONAL MEDICINE) LÖSER C, KEIM V, ESPEN (EUROPEAN SOCIETY FOR PARENTERAL AND ENTERAL NUTRITION). ESPEN Guidelines on Enteral Nutrition : *Pancreas. Clin. Nutr.*, 2006, **25** : 275-84.
16. GOU S, YANG C, YIN T, *et al.* Percutaneous Catheter Drainage of Pancreatitis-Associated Ascitic Fluid in Early-Stage Severe Acute Pancreatitis. *Pancreas*, 2015, **44** : 1161-2.
17. ZEREM E, IMAMOVIĆ G, OMERVIĆ S, IMŠIROVIĆ B. Randomized controlled trial on sterile fluid collections management in acute pancreatitis : should they be removed? *Surg. Endosc.*, 2009, **23** : 2770-7.
18. SUGIMOTO M, SONNTAG DP, FLINT GS, *et al.* A percutaneous drainage protocol for severe and moderately severe acute pancreatitis. *Surg. Endosc.*, 2015, **29** : 3282-91.
19. DA COSTA DW, BOERMA D, VAN SANTVOORT HC, *et al.* Staged multidisciplinary step-up management for necrotizing pancreatitis. *Br. J. Surg.*, 2014, **101** : e65-79.
20. BABU RY, GUPTA R, KANG M, BHASIN DK, RANA SS, SINGH R. Predictors of surgery in patients with severe acute pancreatitis managed by the step-up approach. *Ann. Surg.*, 2013, **257** : 737-50.
21. BRISINDA G, VANILLA S, CROCCO A, *et al.* Severe acute pancreatitis : advances and insights in assessment of severity and management. *Eur. J. Gastroenterol. Hepatol.*, 2011, **23** : 541-51.
22. WU BU, JOHANNES RS, SUN X, TABAK Y, CONWELL DL, BANKS PA. The early prediction of mortality in acute pancreatitis : a large population-based study. *Gut*, 2008, **57** : 1698-703.
23. PAPACHRISTOU GI, MUDDANA V, YADAV D, *et al.* Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am. J. Gastroenterol.*, 2010, **105** : 435-41.
24. ISENMANN R, RÜNZI M, KRON M, *et al.*, German Antibiotics in Severe Acute Pancreatitis Study Group. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis : a placebo-controlled, double-blind trial. *Gastroenterology*, 2004, **126** : 997-1004.
25. RANSON JH, SPENCER FC. The role of peritoneal lavage in severe acute pancreatitis. *Ann. Surg.*, 1978, **187** : 565-75.
26. MAYER AD, MCMAHON MJ, CORFIELD AP, *et al.* Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. *N. Engl. J. Med.*, 1985, **312** : 399-404.
27. ZEREM E, PAVLOVIĆ-ČALIĆ N, SUŠIĆ A, HARAČIĆ B. Percutaneous management of pancreatic abscesses : long term results in a single center. *Eur. J. Intern Med.*, 2011, **22** : e50-4.
28. FOGGIO EJ, GORELICK F. Abdominal Paracentesis Drainage : Which Patients With Severe Acute Pancreatitis Will Benefit? *J. Clin. Gastroenterol.*, 2015, **49** : 717-9.