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Interventional management of necrotizing pancreatitis: an Australian experience

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Key words
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Abstract

Background: The interventional management of necrotizing pancreatitis has evolved from early open surgery to delayed endoscopic or percutaneous intervention. However, few studies have directly compared the three treatment modalities. We aim to compare the outcomes of patients who had endoscopic, percutaneous or surgical interventions for necrotizing pancreatitis at our institution.

Methods: This is a retrospective cohort study of patients who had interventions for necrotizing pancreatitis at our institution from 2005 to 2014. Primary outcome was length of stay (LOS); secondary outcomes were complication rate and number of procedures required for resolution of necrosis.

Results: Thirty patients were included. Mortality rate was 13% (four patients). Median LOS and time to intervention was 88 and 28 days, respectively. There were no significant differences in the computed tomography severity indices and 48-h C-reactive protein levels among the three groups. Initial endoscopic intervention was associated with a median LOS of 62 days compared with 101 days in the percutaneous group and 91 days in the surgical group ($P = 0.04$). There were higher rates of pancreatic fistulae (40%) ($P = 0.012$) and new onset diabetes (30%) ($P = 0.046$) in the surgical group. Median number of procedures was similar among the three groups. Median LOS for patients with delayed intervention (fourth to sixth week of pancreatitis) was 66 days, compared with 137 days in patients with early intervention (first to third week) and 104 days in patients with late intervention (seventh week onwards) ($P \leq 0.001$).

Conclusion: A delayed, endoscopy first approach appears to be a reasonable strategy as it is associated with decreased LOS and low complication rate.

Introduction

Pancreatic and/or peripancreatic necrosis occurs in approximately 5–10% of cases of acute pancreatitis.[1] About a third of patients with necrotizing pancreatitis develop infection of necrosis and this increases mortality from 17 to 39%.[2] Confirmed or suspected infected necrosis is the primary indication for intervention in necrotizing pancreatitis, whereas sterile necrosis with symptomatic bowel or biliary obstruction is secondary indication.[2,3]

The interventional management of necrotizing pancreatitis has evolved throughout the years, from primary open necrosectomy to that of a 'step-up' approach, consisting of initial percutaneous drainage, followed by minimally invasive necrosectomy via the drainage tract if needed.[4,5] The PANTER study was a randomized controlled trial that compared primary open necrosectomy with the step-up approach.[4] It demonstrated a reduction in the major complication rate from 69% in the open necrosectomy group to 40% in the step-up approach group.[4]

Endoscopic necrosectomy is a treatment modality that is gaining traction in the international literature, with a recent systematic review reporting 81% treatment success with endoscopic treatment alone, a mortality rate of 6% and a complication rate of 36%.[6] However, a survey of members of the Australian and New Zealand Hepatopancreaticobiliary Association[7] and a recent letter to the

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editor of the *ANZ Journal of Surgery* suggests that the endoscopic approach is relatively uncommon in Australia and New Zealand.[8]

Few studies have directly compared the effectiveness of these three different treatment modalities in the successful treatment of pancreatic necrosis. To our knowledge, this is the first such series to be reported in Australia.

Apart from the type of treatment modality, the timing of intervention is another vital aspect in the management of necrotizing pancreatitis. A landmark study published in 1997 presented data that early necrosectomy (in the first 48–72 h of pancreatitis) had a 3.4 times higher odds ratio for mortality than late necrosectomy (at least 12 days from the onset).[9] Thus, there has been a shift in the principles of treatment, from early aggressive surgical debridement of necrosis to delayed intervention (at least 3–4 weeks post-onset of pancreatitis) following medical stabilization.[3,10] A 2007 retrospective study showed that postponing necrosectomy until 30 days after admission was associated with decreased mortality.[11]

The aim of this study was to compare the outcomes of a retrospective cohort of patients with necrotizing pancreatitis, who had undergone different initial interventions (endoscopic, percutaneous and surgical) at different time periods (early, delayed and late) during the course of their disease.

Methods

This was a single-centre study conducted in a tertiary hospital in Melbourne, Australia. All patients who underwent endoscopic, percutaneous or surgical interventions for pancreatic necrosis between January 2005 and December 2014 were identified via the relevant Medicare Benefits Schedule item numbers. We reviewed the clinical, pathology and radiology records of these patients. A radiologist with a subspecialty interest in abdominal imaging retrospectively reviewed the contrast-enhanced computed tomography (CT) scans to assess and calculate the modified CT severity index (CTSI) scores for each patient. The dimensions, area and average density (measured in hounsfield units, HU) of each collection were estimated using a picture archiving and communication system-based freehand region of interest tool on the pre-intervention CT scans.

The procedure details for each intervention modality may be found in Appendix S1.

End points and statistics

Patients were analysed based on the type and timing of initial intervention. The primary outcome assessed was the length of hospital stay (LOS). Secondary outcomes were the number of procedures needed and major complication rate. The 48-h C-reactive protein (CRP) levels and the modified CTSI scores were recorded for each patient.

Treatment success was defined as a reduction in volume of the necrotic collection to the point where the patient was asymptomatic and was able to be discharged safely.

Statistical analysis was performed with SPSS version 23 (Chicago, IL, USA). Continuous variables following a skewed distribution were tested for differences using the Kruskal–Wallis test.

Results

A total of 30 patients were included in the study. Twenty-four were male (80%) and the mean age was 60 years old. There were four deaths (mortality rate of 13%). The median LOS of survivors was 88 days (range, 43–402 days). The median time to initial intervention was 28 days (range, 6–72 days). The median number of procedures performed per surviving patient was 2.5. The baseline characteristics of the patients in the study are displayed in Table 1.

Outcomes by type of initial intervention

In terms of type of initial intervention procedure, 40% were endoscopic, 27% were percutaneous and 33% were surgical. There were no significant differences between these groups with regard to 48-h CRP levels and modified CTSI scores.

Twenty-seven out of the 30 (90%) patients had interventions for suspected infected necrosis. One patient with suspected infected necrosis also had suspected ischaemic bowel, which was therefore an indication for open surgery. The remaining three patients had interventions for failure to progress due to gastric outlet obstruction.

Six of the eight patients who underwent initial percutaneous drainage had collections that extended into sites not easily by endoscopic transgastric or transduodenal drainage, such as the subphrenic, subhepatic and paracolic locations (Table S1).

The radiodensity of each collection was used as a surrogate marker of the amount of solid and fluid in each collection. Although

Table 1 Baseline characteristics of patients

	Endoscopic (n = 12)	Percutaneous (n = 8)	Surgical (n = 10)	P-value
Male sex, no. (%)	8 (67)	6 (75)	10 (100)	0.153
Median age, years (range)	69 (31–81)	60 (32–72)	56 (37–77)	0.320
Aetiology, no. (%)				
Gallstones	8 (67)	2 (25)	5 (50)	0.205
Alcohol	0	1 (12.5)	2 (20)	0.343
Post-ERCP	1 (8)	1 (12.5)	1 (10)	1.0
Unknown/others	3 (25)	4 (50)	2 (20)	0.370
Median CT severity index (range)	9 (5–10)	7 (5–10)	8 (3–10)	0.537
Median CRP at 48 h from admission (range)	320 (212–525)	222 (46–469)	370 (74–462)	0.207
Median collection density in HU (range)	13 (–4 to 33)	22 (12–31)	22.5 (11–29)	0.124

CRP, C-reactive protein; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; HU, hounsfield units.

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Table 2 Primary and secondary outcomes

	Endoscopic (n = 12)	Percutaneous (n = 8)	Surgical (n = 10)	P-value
Median LOS in survivors (range)	62 (43–125)	101 (72–184)	91 (47–402)	0.040
Median no. of procedures in survivors (range)	2 (1–5)	3 (1–5)	2 (1–17)	0.462
Major complication rate, no. (%)				
Pancreatico-/enterocutaneous fistula	0	0	4 (40%)	0.012
New onset diabetes	0	0	3 (30%)	0.046
Visceral perforation	0	1 (12.5%)	1 (10%)	0.513
Intra-abdominal bleeding	1 (8.3%)	0	1 (10%)	1.0
Arterial pseudoaneurysm	2 (16.6%)	1 (12.5%)	0	0.604
Readmission	2 (16.6%)	2 (25%)	1 (10%)	1.0
Death	3 (25%)	0	1 (10%)	0.363

LOS, length of stay.

Table 3 Outcomes associated with timing of intervention

	Early (n = 7)	Delayed (n = 19)	Late (n = 4)	P-value
Median CT severity index (range)	8 (3–10)	7.5 (7–10)	8.5 (6–10)	0.933
Median CRP at 48 h from admission (range)	329.5 (53–462)	319 (74–525)	385 (46–469)	0.821
Median LOS in survivors	137	66	104	<0.001
Median no. of procedures in survivors	5	2	3	0.141
Deaths (%)	0	3 (15.8%)	1 (25%)	0.573

CRP, C-reactive protein; CT, computed tomography; LOS, length of stay.

the median HU of the collections (Table 1 and S1) in the endoscopic group appeared slightly lower than in the percutaneous or surgical group, it was not a statistically significant difference (P = 0.124).

Table 2 demonstrates the outcomes based on the type of initial intervention. In patients who underwent initial endoscopic intervention, the median LOS in survivors was 62 days, which was the lowest among the three groups (P = 0.04). Although the median number of procedures required for successful treatment was similar among the three groups, there was a much larger range in the numbers of procedures in the surgical group, ranging from 1 to 17 procedures.

In terms of major complications, the surgical group had high rates of pancreatico-/enterocutaneous fistulae and new onset diabetes mellitus, with 40% (P = 0.012) and 30% (P = 0.046) of patients in the group having these complications, respectively. All three groups had similar rates of readmission (20–25%). The reason for readmission for all readmitted patients was symptomatic recurrence of the necrotic collection. The mortality rate in the endoscopic group (25%) was higher than in the percutaneous (0%) and surgical (10%) groups, respectively. However, this was not a statistically significant difference. The causes of mortality in the endoscopic group were large bowel infarction, pulmonary embolism and acute liver failure – all of which were not directly related to the procedure.

Of the 12 patients who underwent initial endoscopic intervention, there were three patients who crossed over to other modalities. Two patients crossed over to open necrosectomy but both eventually died. One patient underwent further percutaneous drainage. There were eight survivors out of the nine patients who underwent exclusive endoscopic intervention.

We performed a subgroup analysis of patients who had undergone only endoscopic interventions. In this subgroup, the median LOS was 60 days and patients required a median of 2 (range, 1–4) endoscopic procedures to successfully treat the walled-off necrosis.

Four patients had transpapillary drainage via a pancreatic duct stent. One patient had initial transpapillary drainage, which was not sufficient to drain the collection and proceeded to endoscopic cystogastrostomy. One patient had an initial open necrosectomy before transpapillary drainage, but subsequently had percutaneous drainage to clear the collection. Two patients had initial percutaneous drainage before transpapillary drainage, but they also did not achieve adequate clearance with this, thus necessitating further procedures.

In the percutaneous group, seven out of eight patients required other treatment modalities. Three crossed over to endoscopic interventions; three crossed over to minimally invasive necrosectomy; one crossed over to open necrosectomy.

The majority of patients (20 out of 26 surviving patients) did not experience reaccumulation of their collections. Two patients had planned readmissions for repeat endoscopic insertion of stents and three patients had unplanned readmissions for symptomatic reaccumulation of necrotic collections, necessitating repeat endoscopic necrosectomies. One patient who had open necrosectomy initially had multiple readmissions for discharging enterocutaneous fistulae, requiring return to theatre.

Outcomes by timing of initial intervention

Table 3 displays the outcomes based on the timing of initial intervention. The groups are divided into early, delayed and late intervention based on the timing of initial intervention in relation to the onset of pancreatitis. Early intervention was within the first 3 weeks of pancreatitis (day 1–21); delayed intervention was in the fourth to sixth weeks of pancreatitis (day 22–42); late intervention was greater than 6 weeks from onset of pancreatitis (day 43 onwards).

The majority of patients had the initial intervention between the fourth to sixth weeks of pancreatitis. A ‘delayed’ intervention was

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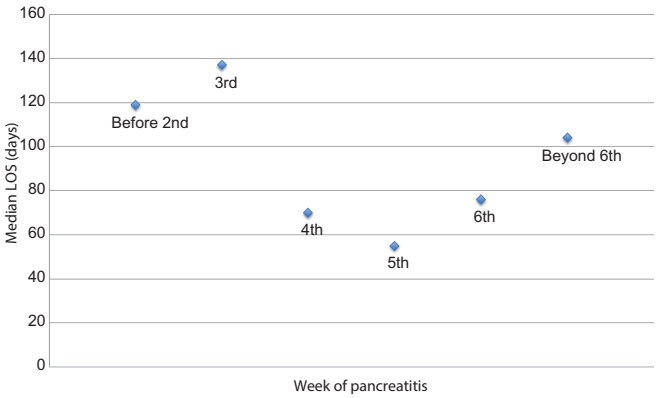

Fig. 1. Median length of stay (LOS) according to timing of intervention.

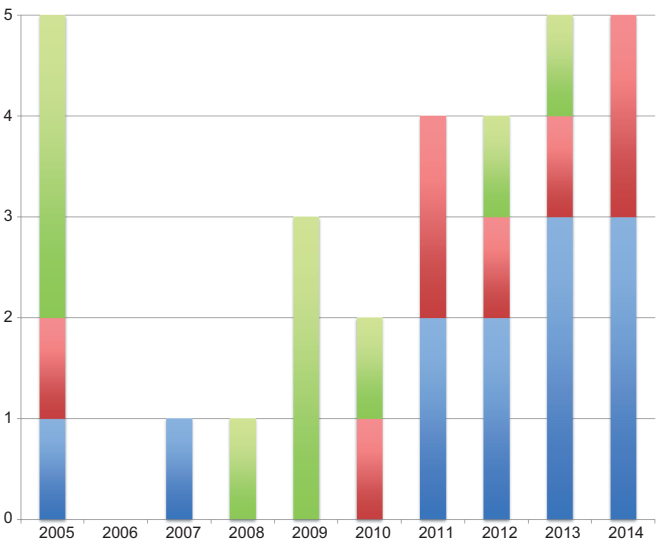

Fig. 2. Type and number of initial intervention by year. (■) Surgical, (■) Percutaneous, (■) Endoscopic.

associated with decreased median LOS in survivors (66 days) ($P < 0.001$) and decreased median number of procedures (2 per patient) ($P = 0.141$).

Figure 1 is a scatter plot of the median LOS of patients grouped by the timing of their initial intervention. It shows a dip in the median LOS in patients with their first intervention in the fourth to sixth weeks of pancreatitis, with intervention in week 5 being associated with the shortest median LOS of 55 days.

Trends in management

Over the 10-year period, the initial treatment modality utilized shifted from primary open necrosectomy to less invasive approaches such CT-guided percutaneous drainage and endoscopic intervention (Fig. 2). In the first half of the series (2005–2009), 70% of the initial interventions were surgical. In contrast, 85% of initial interventions in the second half (2010–2014) were percutaneous (35% of total) and endoscopic (50% of total).

Discussion

This study describes the outcomes of and the trends in the management of acute necrotic collections and walled-off necrosis in a single tertiary institution in Australia. There was a statistically significant reduction in the LOS that was associated with initial endoscopic intervention ($P = 0.04$).

Initial surgical intervention was associated with high rates of morbidity, with pancreatico-/enterocutaneous fistulization ($P = 0.012$) and new onset diabetes mellitus being ($P = 0.046$) more common in the surgical group, compared with the endoscopic and percutaneous groups. This finding is consistent with the current literature.[12–14] There were no significant differences in the rates of other complications among the three groups. Although the mortality rate in the endoscopic group was the highest, the causes of death were not linked to periprocedural complications associated with endoscopic intervention.

There was decreased LOS associated with a delayed (fourth to sixth week of pancreatitis) intervention strategy. To our knowledge, there is currently no literature reporting an association between timing of initial intervention and LOS; thus, further studies might be warranted to test the validity of this finding. Although previous studies have demonstrated a decrease in mortality in patients with initial interventions 4 weeks[11] and 6 weeks[15] from the onset of pancreatitis, respectively, our results did not corroborate with this, with all four of the deaths occurring in patients who had interventions from the fourth week of pancreatitis onwards.

These three treatment modalities are not always competing but can be complimentary. Some collections are not easily accessible endoscopically (e.g. paracolic gutter and flank collections)[16,17] and may be more amenable to a percutaneous approach. A percutaneous approach may also be favoured in patients who require an intervention very early in the disease process, before the collection is sufficiently walled-off to allow endoscopic transmural access. In cases of visceral infarction or perforation, or abdominal compartment syndrome, surgery is clearly the preferred treatment modality.[5] In the absence of difficult endoscopic access and the severe complications necessitating emergent surgery, it is our opinion that endoscopic drainage has theoretical advantages over the other two treatment modalities of (i) being less invasive than surgery and (ii) allowing more effective, prolonged and definite drainage than percutaneous drainage due to the shorter and wider tract.

The main limitations of this study are the relatively small sample size and that patients crossed over between treatment modalities (e.g. a patient who had endoscopic necrosectomy initially might subsequently undergo percutaneous drainage). However, as discussed in the results section earlier, patients in the endoscopic group who had endoscopic interventions exclusively did seem to have even shorter LOS and required even fewer procedures. Our series did include three patients who underwent CT-guided percutaneous drainage initially, then 'stepped-up' to minimally invasive necrosectomy via the drainage tract. Unfortunately, we did not experience the same level of success as the PANTER study group in regard to reducing the LOS and complication rate with the 'step-up' approach.[4] Also, contrary to the findings from a 2011 systematic review, in which percutaneous drainage alone was sufficient 55.7%

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of the time,[18] only one out of the eight patients (12.5%) with initial percutaneous drainage was treated with that modality alone.

Another limitation of the retrospective nature of this study is that temporal factors relating to improved intensive care management and changing paradigms might have had an effect on the reduced LOS experienced by patients in the endoscopic group.

Our results are consistent with the current literature in showing the trend towards delayed intervention using minimally invasive strategies for drainage of necrotic collections in necrotizing pancreatitis.[19] An endoscopy first approach may be a safe and effective strategy, as evidenced by its association with a shorter LOS and a low rate of high-morbidity complications such as pancreatico-/enterocutaneous fistulae and pancreatic endocrine insufficiency. Further large-scale randomized controlled trials (such as the TENSION trial; ISRCTN09186711)[20] would be able to better define the role of therapeutic endoscopy in necrotizing pancreatitis and whether it is indeed a superior modality in terms of safety and effectiveness.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Indications and type of intervention, and radiological characteristics of each collection.

Appendix S1. Procedure details for each intervention.

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