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Multiple interventions with prolonged length of stay are required for treatment of necrotizing pancreatitis

Hamish Shilton, Daniel Breen, Sachin Gupta, Peter Evans and Charles Pilgrim

Department of Surgery, Frankston Hospital, Peninsula Health, Melbourne, Victoria, Australia

Key words

critical care, delivery of health care, pancreatitis, pancreatitis, acute necrotizing, patient care management.

Correspondence

Dr Hamish Shilton, Department of Surgery, Frankston Hospital, Peninsula Health, 2 Hastings Road, Frankston, Vic. 3199, Australia.

Email: hamishshilton@hotmail.com

H. Shilton MBBS; **D. Breen** MBBS; **S. Gupta** MBBS, FCICM; **P. Evans** MBBS, FRACS; **C. Pilgrim** MBBS (Hons), FRACS, PhD.

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Abstract

Background: A proportion of patients with acute pancreatitis (AP) develop necrosis. Around a third will become infected, and this is associated with a significant requirement for intervention and support. We evaluated the burden of necrotizing pancreatitis (NP) in an Australian tertiary hospital with regards to morbidity, mortality and resource consumption.

Methods: This is a retrospective case series of patients with AP admitted for at least 5 days to identify those with NP between 2009 and 2014. Data were analysed in groups according to the determinant-based classification of AP severity.

Results: Of 1339 patients with AP, 546 stayed 5 days or longer, and 38 had necrosis. Overall mortality for those with necrosis was 10.5% (4/38). Infection complicated necrosis in 45% (17/38). Organ failure also occurred in 45% (17/38) of patients with necrosis. All patients in the critical category and severe category required admission to the intensive care unit for a median of 21 and 12 days, respectively. A total of 90% of patients with critical category disease developed multi-organ failure, whereas most with severe category disease developed single organ failure only. Overall length of stay increased with increasing severity of disease. Intervention was required in 82% of infected necrosis (median 4 procedures). Those without infection also required multiple radiological investigations (median 7).

Conclusion: Necrosis is uncommon in our cohort but is associated with a significant health-care burden. Almost half the patients with necrosis develop organ failure requiring prolonged hospital and intensive care unit stay. Patients require multiple investigations and interventions for infected necrosis. NP remains a costly, morbid disease in our society.

Introduction

Acute pancreatitis (AP) is a commonly encountered clinical entity, affecting 68 per 100 000 in 2003.[1] Between 4 and 47% of patients with AP can be expected to develop necrosis, with the rate of infected necrosis reported between 16 and 47%.[2,3]

Necrotizing pancreatitis (NP) is often associated with transient or ongoing single or multi-organ failure, potentially requiring admission to the intensive care unit (ICU); repeated imaging, particularly when necrotic tissue becomes infected; and repeated percutaneous, endoscopic or surgical drainage or debridement. This incurs a significant expense on health-care resources. Although recent advances in management, namely less invasive 'step-up' approaches, have moved surgeons away from the early and widespread application of laparotomy, this disease remains resource intensive.

Despite advances in care, recent Australian data reveal a mortality of 13% and a length of stay of 3 months for patients with NP.[4] Infected necrosis is associated with a mortality rate in the range of 8–39%.[5]

This study aims to evaluate the burden of this illness in terms of patient morbidity and mortality as well as resource consumption in a tertiary hospital in the metropolitan Australian setting.

Methods

Ethics approval was obtained. Patients with a diagnosis of pancreatitis were identified by a hospital coding search over 5 years, between June 2009 and June 2014, at Frankston Hospital. Those with pancreatitis staying at least 5 days were identified, assuming those with a length of stay (LOS) less than 5 days were unlikely to have NP, and this formed the cohort for this study. Patient histories were reviewed, and instances of computed tomography (CT) imaging, magnetic resonance imaging (MRI) and positive pancreatic tissue and fluid microscopy and cultures were retrieved to identify those

Table 1 Determinant-based classification of acute pancreatitis severity

	Mild	Moderate	Severe	Critical
(Peri)pancreatic necrosis	No	Sterile	Infected	Infected
	AND	AND/OR	OR	AND
Organ failure	No	Transient	Persistent	Persistent

with necrotizing and/or infected pancreatitis. Further data regarding the nature and timing of interventions, presence and severity of organ failure and overall and ICU length of stay were recorded. Patients were then retrospectively grouped according to the established Determinant-Based Classification of Acute Pancreatitis Severity (Table 1), and the American Society of Anesthesiologists Physical Status Classification System score, calculated as a surrogate of systemic illness.[6,7]

We defined renal failure as requiring renal replacement therapy, cardiac failure as requiring inotropic support and respiratory failure as requiring invasive ventilation.

Statistical analysis

Data are presented as mean ± standard deviation and median (interquartile range) as appropriate. To compare the difference between LOS between multiple groups, one-way analysis of variance with Scheffe's *post hoc* correction was used in Stata (Stata Statistical Software: Release 14; StataCorp LP, College Station, TX, USA). Significance level was set at 0.05.

Results

There were 1339 patients diagnosed with pancreatitis by coding between 2009 and 2014. A total of 546 had a stay of 5 days or longer. The medical records and imaging results of these patients were reviewed for evidence of necrotizing disease; 38 patients were confirmed to have NP on CT or MRI and were further evaluated (Fig. 1).

Baseline characteristics are presented in Table 2. There was a male predominance in our cohort (68%), with alcohol more frequently the cause in males and gallstones in females, but this was not statistically significant. After characterizing whether patients developed transient or ongoing organ failure, and whether necrosis was sterile or infected, there were 18 patients categorized as moderate and 10 each with severe and critical severity AP.

Table 2 Baseline characteristics

	Moderate	Severe	Critical	Overall
Number (%)	18 (47.4)	10 (26.3)	10 (26.3)	38 (100)
Age, mean (SD)	47.9 (19.6)	57.2 (15.2)	53 (21.1)	51.6 (18.7)
Gender, male (%)	12 (66.7)	8 (80)	6 (60)	26 (68.4)
ASA score (median)	2	2.5	2.5	2
Aetiology, *n*				
Alcohol	10	3	4	17 (44.7)
Gallstones	5	5	4	14 (36.8)
ERCP	0	0	1	1 (2.6)
Other	1	1	0	2 (5.2)
Idiopathic	2	1	1	4 (10.5)

ASA, American Society of Anesthesiologists; ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation.

Length of stay and development of complications are presented in Table 3. Length of stay increased with worsening severity in terms of total days in hospital and in ICU admission. Moderate severity patients required the ICU for a median of less than 1 day, whereas critical severity patients were admitted to the ICU for a median of 21 days. Median overall hospital LOS increased from 10 to 50 to 67 days for moderate/severe/critical severity, respectively. Re-admission for patients with NP was common, occurring in 28% of moderate severity patients, 40% of severe and 30% of critical patients.

Sterile versus infectious necrosis

Slightly less than half of the patients with NP developed infected necrosis (n = 17, 45%). Infected necrosis was identified by CT findings alone in seven patients (defined by free gas in a pancreatic or peripancreatic collection), positive fine-needle aspiration (FNA) microscopy and culture in five patients and positive necrosectomy culture in five patients. Organisms isolated from pancreatic tissue collected via any route were a mixture of yeast, gram-positive

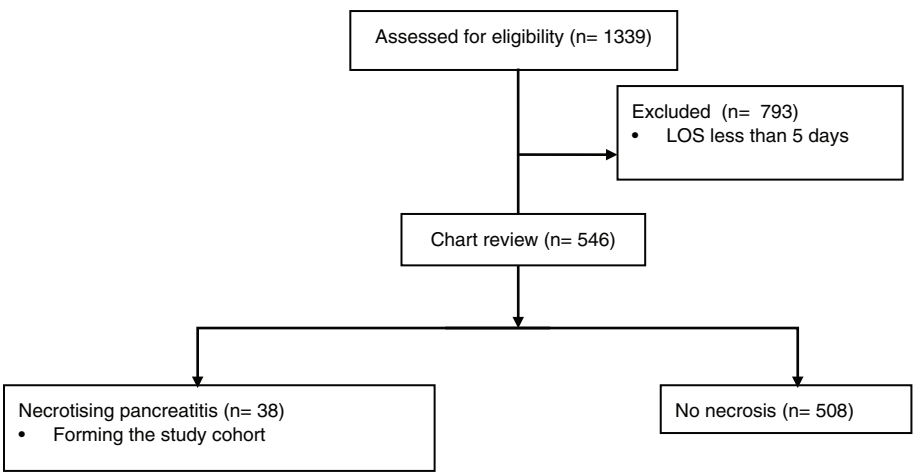

Fig. 1. Inclusion flow chart. () No. of patients.

Table 3 Length of stay and rate of complications amongst patients with necrotising pancreatitis

	Moderate (*n* = 18)	Severe (*n* = 10)	Critical (*n* = 10)	Overall (*n* = 38)
Length of stay, median (IQR)				
LOS total, days*	10 (8, 17.25)	49.5 (40, 58.5)	66.5 (46.75, 97.25)	21.5 (10, 50.75)
LOS ICU, days**	0	11.5 (6.25, 19.5)	21 (10, 45.5)	3.5 (0, 14.5)
Day necrosis diagnosed	4 (2, 4.5)	11 (8, 16)	6 (3.25, 8.5)	4 (2, 8)
Complications, *n*				
Infection	2	6	10	28
Renal failure	0	5	9	14
Respiratory failure	0	2	7	9
Cardiac failure	0	2	9	11

*P = <0.001. **P = <0.001. ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

and gram-negative bacteria (Enterococcus 11, *Candida* species 5, *Escherichia coli* 3, mixed anaerobes 2, Pseudomonas 2, Klebsiella, single isolates each of Staphylococcal species, Stenotrophomonas, Citrobacter and bacteroides).

Organ failure

Organ failure is a determinant of severity of disease. It occurred in 45% (17/38) of all patients with necrosis. It was seen in 70% (7/10) of patients' categorized as severe and (by definition) 100% (10/10) of patients with critical disease. Patients who have critical disease were, however, more likely to have multi-organ failure than those with severe disease (90% versus 20% multi-organ failure, respectively). Single organ failure was seen more commonly in the severe category (50% versus 10% of the critical category).

Imaging

The number of investigations and interventions is summarized in Table 4. Worsening severity disease is accompanied by increased number of required investigations, including CT, ultrasound and MRI for diagnosis and assessment of progression, as well as radiologically guided interventions. All patients with NP required multiple investigations (median = 7.5). Moderate severity patients required a median of one CT compared to eight in severe and nine in critical disease.

Interventions

When comparing patients with sterile (moderate classification) and infected necrosis (severe or critical classifications), patients with infected necrosis underwent significantly more interventions. Overall, 45% (17/38) patients with NP underwent some form of intervention, while 82% (14/17) of patients with infected NP required intervention of any form. Most patients requiring intervention underwent multiple procedures (median = 2), most frequently percutaneous drains, which remained *in situ* for a median of 34 days. Critical severity patients required more interventions than severe and moderate patients, of which most were percutaneous drains (60%) and open procedures (50%), whilst severe patients largely required endoscopy (50%) rather than percutaneous drains (20%) or an open procedure (20%). Minimally invasive procedures were performed in one severe and one critical severity patient (10%).

Table 4 demonstrates the total number of these interventions performed on all patients, and Figure 2 demonstrates the frequency of interventions performed per patient. Most patients required none or one procedure, but eight patients (21%) required four or more interventions.

Outcome

Overall mortality for our cohort was 10.5% (4/38), with three deaths in those with critical disease and one death in a patient with severe disease. Three patients were transferred from our institution, one requiring extra-corporeal membrane oxygenation on day nine,

Table 4 Investigations and interventions in patients with necrotizing pancreatitis

	Moderate (*n* = 18)	Severe (*n* = 10)	Critical (*n* = 10)	Overall (*n* = 38)
Investigations, median per patient				
CT	2	8	9	4
US	1	2	3	2
MRI	0	1	1	1
Interventions, *n*				
Radiological	1	8	18	27
Endoscopic	1	10	4	25
Minimally invasive surgical procedure	0	1	1	2
Open surgical procedure	0	2	5	7
Discharge disposition, *n* (%)				
Home	17 (94.4)	4 (40)	3 (30)	24 (63.2)
Rehab	1 (5.6)	4 (40)	2 (20)	7 (18.4)
Transfer	0	1 (10)	2 (20)	3 (7.9)
Death	0	1 (10)	3 (30)	4 (10.5)

CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

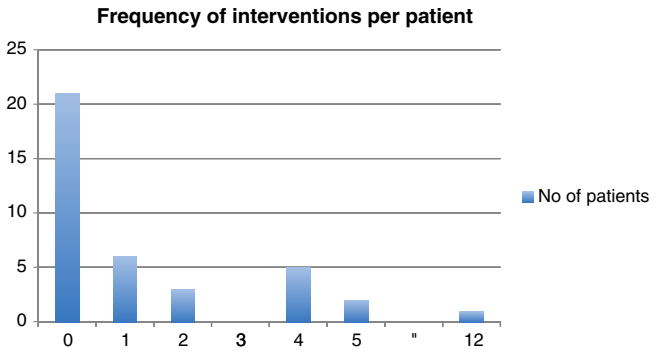

Fig. 2. Frequency of interventions (number of interventions for individual patients, *x* axis = number of interventions per patient, *y* axis = number of patients).

one patient with a lung transplant on day six for co-management with the transplant respiratory unit, the third patient was transferred at day 61, after 50 days in ICU, after developing mesenteric and portal vein thrombosis. All survived.

Discussion

These data reflect the specific burden that NP has on a typical tertiary hospital in Australia, showing that this is indeed a disease associated with prolonged stay and multiple episodes of utilization of radiological, endoscopic and surgical services.

We used the determinant-based classification (DBC) of AP severity for our data collection based on the local and systemic determinants of severity in AP.[6] The local determinant is the presence of (peri)pancreatic necrosis and whether this is sterile or infected. Systemic determinants relate to the presence of organ dysfunction and whether this is transient or persistent. The DBC has been compared to the revised Atlanta classification and performs equally well for the classification of AP with the addition of identifying those with the most severe disease.[8,9]

Our overall mortality was similar to that reported in a recent multicentre observational study of 15% and similar to recent Australian experience reporting mortality of 13%.[4,10] This compares favourably to the mortality of up to 39% reported in some studies.[3] The Australian health-care system is such that patients with severe disease admitted to rural or regional hospitals are often transferred to tertiary institutions for specialist management where higher levels of intensive care and intervention may be available. The most severe cases are therefore concentrated in specialist units, frequently managed by dedicated hepatobiliary surgeons; however, we did not collect data regarding day of transfer to our unit. Severe cases are also readily managed in an high dependency unit or ICU setting in Australia, which may reduce mortality compared to ward-managed patients.[11]

Patients with critical or severe NP required inpatient care for a median of 67 and 50 days, respectively, and even patients diagnosed with moderate severity disease (sterile NP without organ failure) had a median total length of stay of 10 days, despite many in this category not requiring intervention. This underlines the hospital resources and bed days occupied secondary to this disease, even for patients without the need for intensive care, and highlights the significant impact the presence of pancreatic necrosis confers on inpatient stay.

Necrosis was generally diagnosed within the first week of presentation (median day four), and these data are consistent with the recommendation to delay initial imaging beyond 72–96 h after onset of symptoms.[12] Unsurprisingly, patients with infected necrosis were more likely to require intervention than those with sterile necrosis. However, these patients were also more likely to have organ failure, during which surgical intervention and further physiological stress should be minimized where possible until resolution of the organ failure as this has been associated with poorer outcomes.[13] Woo *et al.* have assessed the timing of first intervention in a cohort with NP and found that the shortest overall length of stay was in patients who had the first intervention between 4 and 6 weeks following onset of AP.[4] A minimally invasive step-up approach to intervention was demonstrated to be superior in the PANTER trial, which randomized 348 patients with NP to open necrosectomy or step-up approach and reported lower rates of major morbidity (including new onset multi-organ failure) in patients with NP treated with the step-up approach.[14] A move towards more minimally invasive intervention is reflected in our practice where there were 27 radiologically placed drains and 25 endoscopic interventions and only 7 open necrosectomies performed.

Radiological and clinical findings may be sufficient to diagnose the infection of necrosis rather than reliance on FNA as this is associated with a false negative rate of 12–25%.[12] However, in our cohort of 17 patients with infected necrosis, five positive FNA cultures and five positive necrosectomy cultures were isolated in patients without presence of gas on imaging (although these patients did have clinical suspicion of infection of necrosis). Whilst CT is widely used to assess evidence of infection, our data suggest that a significant number of patients without definite evidence of infection on CT would have culture-proven infection if FNA were performed. A combination of clinical findings, radiological appearance and FNA in cases of doubt would appear prudent rather than abandoning FNA altogether.

Prophylactic antibiotic administration remains controversial in the management of acute NP with a recent meta-analysis still showing conflicting data.[15,16] The 2012 working group of the International Association of Pancreatology/American Pancreatic Association acute pancreatitis guidelines do not recommend prophylactic antibiotic use.[12] In clinical practice, it is very difficult to avoid administering antibiotics to patients in the intensive care setting as virtually all patients have markers of the acute inflammatory process of pancreatitis (i.e. fever, raised white cell count, raised C-reactive protein etc), which can be difficult to distinguish from the true infection of necrosis.

Infected necrosis without drainage results in a mortality approaching 100%.[17] The use of antibiotics and drainage for necrotizing disease in the absence of gas on imaging is supported if suspicion of infection exists. Suspected infected necrosis may be defined as persistent sepsis or progressive clinical deterioration despite maximal support in the ICU, without documentation of infected necrosis.[14] With the step-up approach, radiological drainage of collections in this context is appropriate and in our series was required in 26% of patients with necrosis at some point during their inpatient stay.

Development of multiple organ failure is associated with prolonged ICU admission and worse outcome. The DBC does not discriminate between single and multiple organ failure, but we did find that those with critical AP were more likely to have multiorgan failure than those with severe AP who tended to have single organ failure only, and this may be another useful determinant to consider when predicting patient course and expectation of outcome.

Limitations of our study relate mainly to its retrospective nature. To narrow our chart review, we limited the search to those patients who had an admission of at least 5 days to exclude those with mild disease. It is extremely unlikely that any patient with NP resolved and was discharged by day four, although it is possible that we missed cases of necrotizing disease resulting in early death, which has been reported as high as 50% of the total mortality.[17] However, as far as we know, there were no such cases during the reported 5-year period. A formal health cost analysis was beyond the scope of this manuscript, but our data clearly show the multiple episodes of radiological investigation and intervention as well as the prolonged length of stay, which are prime determinants of health costs.

Conclusion

This study found that the mortality rate associated with NP in our cohort was 10.5%. Over half required some form of drainage procedure, with minimally invasive procedures predominating. Overall, as AP is increasingly complicated by necrosis, infection and organ failure, patient-centred and health-care delivery metrics increase proportionally. The DBC, which builds on the modified Atlanta classification, provides a simple framework to assess patient severity, and a step-up approach to management appears to improve outcome compared with earlier literature. This disease results in prolonged LOS and heavy utilization of radiological and intensive care services and continues to have a high mortality.

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