Factors influencing morbidity and mortality in acute pancreatitis; an analysis of 279 cases

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Abstract

Of 279 patients admitted to a specialist unit with acute pancreatitis, 210 were admitted directly and 69 were transferred for treatment of local or systemic complications. Outcome was assessed in terms of mortality and morbidity and in relation to aetiology, predicted severity of disease (modified Glasgow score), organ failure (modified Goris multiple organ failure score), and need for surgical intervention. The death rate was 1·9% in patients admitted directly but was 18·8% in those transferred from other units. Mortality in gall stone related pancreatitis was 3% compared with 15% (p=0·03) in pancreatitis of unknown aetiology and 27% (p=0·01) in post-endoscopic retrograde cholangiopancreatography pancreatitis. Mortality was related to age (mortality >55 years old 11% *v* 2%; p=0·003) and Goris score (score 0, mortality 0% *v* score 5–9, mortality 67%; p=0·001). In patients transferred from other units, mortality was 11% in those transferred within a week of diagnosis and 35% when transfer was delayed (p=0·04). Thirty six patients had pancreatic necrosis on dynamic computed tomography of whom 29 underwent pancreatic necrosectomy with a 34% mortality. Mortality was related to the modified Goris score (median score 2 in survivors *v* 6 in non-survivors; p=0·005) and was higher when necrosectomy was performed within the first two weeks of admission (100% *v* 21%; p=0·004). In conclusion, mortality in acute pancreatitis is influenced by age, aetiology of the disease, and presence of organ failure. Patients transferred for specialist care have a 10-fold greater mortality than those admitted directly and mortality is greatest when transfer is delayed. Early necrosectomy carries a prohibitively high mortality.

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Acute pancreatitis remains a common and potentially lethal disease. Although conservative treatment results in rapid recovery in most cases, a proportion of patients develop extensive pancreatic inflammation and necrosis, a systemic inflammatory response, and multiple organ failure. This significant minority pose difficult management problems and they often have a protracted hospital stay, need intensive care, and require major surgery to deal with the consequences of pancreatic necrosis.[1]

Despite apparent improvement in the mortality of acute pancreatitis in recent years[2 3] various subgroups of patients remain at increased risk. The elderly may pose particular difficulty because of the high frequency of intercurrent disease and reduced organ functional reserve,[4] and there is evidence that patients with idiopathic pancreatitis[5] and the obese[6] also have a worse prognosis. Pancreatitis developing after surgery is a rare but dangerous event, and while pancreatitis complicating endoscopic retrograde cholangiopancreatography (ERCP) is generally mild,[7] deaths are occasionally recorded.

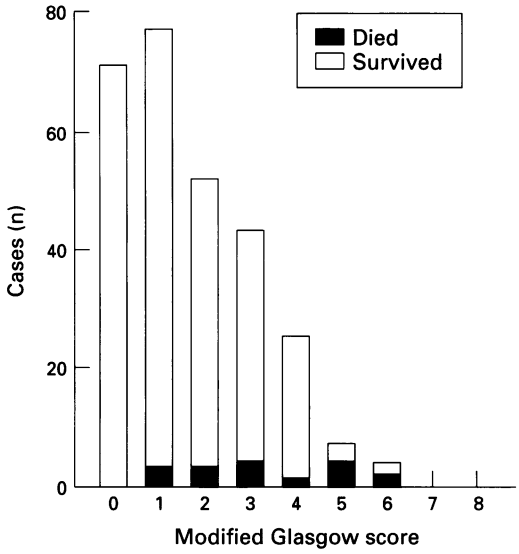
This paper examines the relation between aetiology, organ dysfunction, and mortality in 279 patients admitted with acute pancreatitis to a specialist unit. Particular attention is directed towards those patients undergoing pancreatic necrosectomy and to the identification of factors associated with a poor outcome.

Patients and methods

During the five year period 1 January 1989 to 31 December 1993, patients with acute pancreatitis admitted to the University Department of Surgery, Royal Infirmary of Edinburgh were identified from copies of the discharge summary held in conjunction with a computerised operation database. The diagnosis of acute pancreatitis was based on the presence of appropriate clinical or radiographic evidence accompanied by a serum amylase concentration greater than 1000 units/l (Phadebas; Pharmacia Diagnostics, Uppsala, Sweden; normal range 70–300 units/l), but in one patient, the diagnosis was made for the first time at postmortem examination. Patients were treated using an established protocol.

Gall stone related disease was based on the identification of gall stones by radiology or ultrasonography. Alcohol related disease was assumed if there was a clear history of alcohol consumption before the attack of pancreatitis and when no other identifiable factors could be identified. Postoperative and post-ERCP pancreatitis was diagnosed if the disease occurred within a week of the procedure. Pancreatitis was classified as idiopathic when an aetiological factor could not be identified.

The severity of pancreatitis was scored within 48 hours of admission using the modified Glasgow method; severe pancreatitis was predicted when the score was 3 or more.[8] A modified Goris multiple organ failure score[9] was calculated. (This scoring system assigns a value of 0, 1, or 2 to the seven main organ



Severity of acute pancreatitis in 279 patients determined by the modified Glasgow score with the mortality in each subgroup.

Data points representing number of patients who died or survived by modified Glasgow score.

Modified Glasgow score	*Died*	*Survived*
0	0	71
1	3	74
2	3	49
3	4	39
4	1	24
5	4	3
6	2	2
7	0	0
8	0	0

systems, namely the renal, respiratory, cardiovascular, hepatic, central nervous, haemopoeitic, and gastrointestinal system based on clinical and investigation findings, with the worse score being 14.) By definition all patients with acute pancreatitis score 2 on the standard Goris score for failure of the gastrointestinal system, but in this report, gastrointestinal failure was based on the remaining criteria of stress ulcer formation, gastrointestinal haemorrhage or necrotising enterocolitis.

Mortality was calculated as the number of patients dying during their index hospital admission with pancreatitis. Morbidity was classified into local pancreatic complications, infective episodes, cardiovascular events, gastrointestinal complications, postoperative events, and miscellaneous complications. Pancreatic complications were defined, based on the Atlanta classification,[10] as: (a) pancreatic necrosis; defined areas of low or absent enhancement on rapid bolus contrast enhanced computed tomography or finding of necrosis at operation; (b) acute fluid collection; collection of fluid located in or near the pancreas without a defined wall on ultrasonography or computed tomography, or at laparotomy early in the course of acute pancreatitis; (c) pancreatic pseudocyst; collection of fluid with a well defined wall on ultrasonography or computed tomography, or at laparotomy four or more weeks from the onset of acute pancreatitis; (d) pancreatic abscess; positive culture from pus obtained by percutaneous aspiration or operative drainage of a pancreatic/peripancreatic collection; (e) pancreatic fistula; fluid recovered from a wound or drain site with an amylase concentration more than twice that of serum, or radiological demonstration of a fistulous connection on injection of contrast into the pancreatic duct or collection. Infective episodes were present when pus was recovered or bacteriological cultures were positive. Cardiovascular events, gastrointestinal and postoperative complications were regarded as significant if they required therapeutic intervention.

Patients requiring operation for pancreatic necrosis underwent blunt necrosectomy at which large bore drains were placed in the lesser sac to permit postoperative irrigation.[11] Samples taken at operation were sent for bacterial culture and antibiotic sensitivity determination and the timing of surgery relative to admission was noted.

Statistical analysis

Groups were compared by Mann-Whitney U test for continuous variables and by Fisher's exact test for categorical variables; statistical significance was assumed when $p<0{\cdot}05$.

Results

Of 279 patients with acute pancreatitis, 210 were admitted directly to the University Department of Surgery and 69 were transferred from other units for treatment of local or systemic complications. The age range was 11 to 92 years with a median age of 53 in the direct admission group and 56 in transferred patients. Men predominated in a ratio of 1·6:1. Most patients had predicted mild disease (200 of 279 cases; 72%) with no organ failure (189 of 279 cases; 68%) but transferred patients more often had severe disease than those admitted directly (45% *v* 23% respectively; $p=0{\cdot}0007$). The Figure shows the predicted severity of acute pancreatitis and its effect on mortality. Ninety patients had a modified Goris multiple organ failure score of 1 or more, 55 patients in the direct admission group and 35 in the transfer group (26% *v* 51% of cases; $p=0{\cdot}003$). The higher the modified Goris multiple organ failure score, the greater the likelihood of death; there were no deaths in the 189 patients who had a score of zero compared with seven deaths (9%) in the 75 patients with a score of 1–4 ($p=0{\cdot}001$), and 10 deaths (67%) in the 15 patients with a score of 5 or more ($p=0{\cdot}001$).

There were four deaths (1·9%) in the direct admission group; two of these patients had idiopathic disease, one patient developed postoperative pancreatitis after a right lobectomy for lung carcinoma and one developed pancreatitis after myocardial infarction. There were 13 deaths (18·8%) in transferred patients, four of whom had gall stone related disease, one had alcohol related disease, three had post-ERCP pancreatitis, four had idiopathic pancreatitis, and one with terminal colonic carcinoma was found to have had acute pancreatitis at postmortem examination. Mortality among transferred patients was adversely

TABLE I *Aetiology of acute pancreatitis in patients admitted directly or transferred from other units*

	Direct admission No (%)	*Transfer admission No (%)*
Gall stones	84 (40)	32 (46)
Alcohol	80 (38)	17 (25)
Idiopathic	30 (14)	11 (16)
Post-ERCP	6 (3)	5 (7)
Pancreatic cancer	4 (2)	1 (1)
After operation	3 (1)	0
Post-myocardial infarction	1 (1)	0
Trauma	1 (1)	0
Metastatic carcinoma and biliary stent	1 (1)	0
Immunosuppressant therapy post-renal transplant	0	1 (1)
Hyperlipidaemia	0	1 (1)
Terminal colon carcinoma	0	1 (1)
Total	210 (100)	69 (100)

influenced by delay in referral. Of the 69 transferred patients, 46 were transferred within the first week of diagnosis with five deaths (11%) compared with eight deaths (35%; p=0·04) in the 23 patients transferred after a week had elapsed from diagnosis. There was no difference between these two subgroups in median age (57 *v* 56 years; p=0·82), modified Glasgow score (median 2, range 0–6 *v* 2, 0–5; p=0·51), and Goris multiple organ failure score (median 1, range 0–8 *v* 0, 0–9; p=0·75).

Table I lists the aetiological factors identified. Gall stones or alcohol were deemed responsible for 78% of attacks in direct admission patients but 14% had no identifiable aetiology. In transferred patients, pancreatitis was most commonly caused by gall stones (46%) but 16% had no defined cause. Table II examines the relation between aetiology and predicted disease severity, organ failure, and mortality. Pancreatitis with alcohol related disease had less severe disease (p=0·01) and lower Goris multiple organ failure scores (p=0·03) than patients with gall stone pancreatitis. Patients with idiopathic and post-ERCP pancreatitis had higher death rates (15%, p=0·03 and 27%, p=0·01 respectively) than those with gall stone pancreatitis (3%).

Sixty three patients (30%) in the direct admission group and 40 transferred patients (58%) required one or more surgical or interventional radiological procedures during their index hospital admission (Table III). ERCP in this context refers to endoscopy performed after the onset of disease and does not include the 11 patients who developed pancreatitis as a consequence of ERCP. Twenty two patients underwent cholecystectomy during the index admission, with or without duct exploration, initially by an open approach but more recently by laparoscopic means.

Seventy four patients (35%) in the direct admission group and 52 patients (75%) in the transfer group developed complications during their hospital stay (Table IV).

Of the 29 patients undergoing necrosectomy, five required one further necrosectomy and one required a third necrosectomy. Eighteen of these patients (62%) had an admission Glasgow score of 3 or more and 23 patients (79%) scored 1 or more on the modified Goris multiple organ failure score. Table V shows the relation between aetiology and predicted disease severity, organ failure, and mortality in patients undergoing necrosectomy. Patients with idiopathic, post-ERCP or alcohol related pancreatitis did not differ significantly from those with gall stone pancreatitis in terms of modified Glasgow score or Goris multiple organ failure score. The mortality of idiopathic (71%) and post-ERCP (100%) pancreatitis in those patients undergoing necrosectomy, however, was significantly greater than that of gall stone pancreatitis (8%). The 10 patients who died had a higher median Goris multiple organ failure score (median 6, range 2–9) than the 19 survivors (median 2, range 0–7; p=0·005) but did not differ significantly in age (median age 68 *v* 58 years; p=0·14). The five patients who underwent necrosectomy within two weeks of diagnosis all died whereas there were five (21%) deaths in the 24 patients when necrosectomy was performed after two weeks (p=0·004). In patients undergoing early necrosectomy, significant intra and postoperative bleeding occurred in three cases, whereas bleeding was problematic (but controllable at further laparotomy) in only one of 24 patients where necrosectomy was performed after two weeks. Seventeen (47%) of 36 patients with pancreatic necrosis had positive bacteriology, but the death rate between those with confirmed infected (24%) and sterile necrosis (32%) was not significantly different (p=0·24).

TABLE II *Incidence of severe disease, organ failure, and mortality according to the aetiology of acute pancreatitis*

Aetiology	*Patients (n)*	*Glasgow score >2 No (%)*	*Goris score >0 No (%)*	*Mortality No (%)*
Gall stone	116	39 (34)	46 (40)	4 (3)
Alcohol	97	16 (16)*	20 (21)*	1 (1)
Idiopathic	41	12 (29)	12 (29)	6 (15)*
Post-ERCP	11	4 (36)	5 (45)	3 (27)*
Pancreatic cancer	5	1 (20)	0 (0)	0 (0)
After operation	3	3 (100)	3 (100)	1 (33)
Post-myocardial infarction	1	1 (100)	1 (100)	1 (100)
Trauma	1	1 (100)	0 (0)	0 (0)
Metastatic cancer	1	0 (0)	0 (0)	0 (0)
Immunosuppressant therapy	1	1 (100)	1 (100)	0 (0)
Hyperlipidaemia	1	0 (0)	1 (100)	0 (0)
Terminal colon cancer	1	1 (100)	1 (100)	1 (100)
Total	279	79	90	17

*p<0·03 Fisher's exact test compared with gall stone pancreatitis.

Discussion

Acute pancreatitis remains a dangerous disease although death rates seem to be falling in recent analyses of national statistics. For example, in Finland the mortality fell from 5·9% to 2·6% in the period 1970 to 1989[3] while in Scotland it fell from 17·8% in 1961 to 5·8% in 1985.[2] These trends may not be reflected in data from individual surgical units receiving a high proportion of patients with complicated and severe disease, and the overall mortality in this study is similar to that of 7·6% reported from Leeds for the years 1985 to 1987.[12] A regional study from the north east of Scotland covering the period 1983–1985 reported a death rate of 15%,[13] but included all deaths from pancreatitis in patients treated by medical as well as surgical specialties, and patients in whom the diagnosis was made for the first time at postmortem examination (as in

TABLE III *Number of interventional procedures performed*

	Direct admission (n=210)	*Transfer admission (n=69)*
Necrosectomy	17	18
Pseudocyst drainage	14	13
Open procedure	5	5
Ultrasound guided	8	8
Via gastroscope	1	0
Fluid collection drainage ultrasound guided	8	4
ERCP	25	16
Cholecystectomy	20	2
Percutaneous gall bladder drainage	1	0
Wound exploration	1	1
	(n=63)	(n=40)

one patient in this review). The need to avoid complacency in our attitude to acute pancreatitis is underlined by an analysis of 126 fatal cases in the period 1974–1984 in Glasgow[14] where in no less then 42% of cases, the diagnosis of pancreatitis was made for the first time at necropsy.

The death rate in this review of 1·9% for the 210 patients admitted directly to our unit must be set against the overall death rate of 6·1%, and a death rate in transferred patients of 19%. There is little information in published works about the effect of timing of referral of patients with acute pancreatitis to a specialist centre, but our findings suggest that delay in transfer is associated with an increased mortality, rising in our experience from 11% to 35% (p=0·04) when transfer was delayed beyond the first week after diagnosis. It is impossible to discover from our data if changes in referral patterns would lead to significant improvements in overall outcome in these ill patients.

Our study has confirmed that the elderly are at greater risk from acute pancreatitis in that mortality overall increased from 2% in those under 55 years of age to 11% in older patients. In a study from Bristol,[15] the death rate for those over the age of 60 years of age was 28% compared with 9% in younger patients, while in Hong Kong[16] mortality increased from 5·9% in those under 50 to 21·3% in the over 75 age group.

Acute pancreatitis of unknown aetiology is also associated with an increased mortality.[5 17] Browder *et al*[5] in a study of patients over 60 found a death rate of 8·3% in those with a defined aetiology compared with 24% in those without. Our overall mortality for patients with idiopathic disease was 13% compared with 4·6% when the aetiology was defined. It is now evident that some of these patients have biliary tract disease and have cholesterol crystals or granules of calcium bilirubinate, or both, in their bile,[18] and that cholecystectomy or endoscopic papillotomy may reduce the risk of recurrent pancreatitis in such cases.[19] Our preliminary experience has been disappointing in that we have seldom identified particular matter in the bile of patients with idiopathic disease, but our study of this aspect of 'idiopathic' pancreatitis continues. Another high risk group in this study were patients with ERCP induced pancreatitis, where there were three deaths out of 11 cases (27%). In these three fatal cases, the serum bilirubin concentration continued to rise after ERCP suggesting continuing obstruction and possibly infection of the biliary tree. Renal failure in these patients was an early event and it is clear that great care must be exercised in fluid balance and in the use of potentially nephrotoxic agents such as non-steroidal anti-inflammatory drugs and intravenous contrast media.[20] The high mortality in our patients with idiopathic and post-ERCP pancreatitis cannot be attributed to age in that these groups were not significantly older than our overall patient population. Alcohol related pancreatitis proved to be generally less severe in its course with only one death in 97 patients in this study.

The modified Glasgow score remains a valuable predictor of disease severity in the early hours after hospital admission. The higher the score, the more likely it is that the patient will develop complications, require surgery or succumb, although patients in whom mild disease is predicted on their initial assessment may still die. The sensitivity and specificity of this score, however, lie in the region of 80%[8] so that a high Glasgow score remains a valuable signal that close observation is required.

Organ dysfunction occurs in around one in four of patients with acute pancreatitis.[12] A spectrum of dysfunction exists in that many more patients suffer organ impairment, including measurable hypoxia, hypotension, and renal insufficiency than meet some arbitrary criteria for organ failure. Tran *et al*[21] found organ failure in 20% of patients with acute pancreatitis, but the criteria used in this study had threshold values that were generally higher

TABLE IV *Type and number of complications in patients admitted directly with acute pancreatitis or transferred from other units*

	Direct admission (n=210)	*Transferred patients (n=69)*
Pancreatic necrosis	15	21
Pseudocyst formation	15	30
Pancreatic abscess	11	8
Acute fluid collection	10	12
Pancreaticocutaneous fistula	2	5
Pancreaticopleural fistula	0	1
Chest infection	22	13
Urinary tract infection	8	6
Central line infection	3	6
Wound infection	7	4
Cholangitis	1	3
Subphrenic abscess	1	0
Lung abscess	1	0
Hepatic abscess	1	1
Empyema gall bladder	0	1
Congestive cardiac failure	5	3
Cardiac arrhythmia	5	3
Myocardial infarction	1	1
Deep venous thrombosis	1	2
Pulmonary embolus	0	2
Pleural effusion (drained)	2	5
Superior vena cava thrombosis	1	0
Parotitis	1	1
Duodenal fistula	2	0
Hepatic haematoma	1	1
Colonic necrosis	1	1
Pseudomembranous colitis	1	2
Anastomotic leak	1	0
Postoperative haemorrhage	2	2
Wound dehiscence	1	0
Delirium tremens	7	2
Symptomatic hypocalcaemia	1	6
Urinary retention	1	1
Urticarial drug reaction	1	0
Dislocated total hip replacement	0	1
	(n=74)	(n=52)

TABLE V *Incidence of disease severity, organ failure, and mortality by aetiology of pancreatitis in patients undergoing pancreatic necrosectomy*

Aetiology	*Patients No (%)**	*Glasgow score >2 No (%)†*	*Goris MOF score >0 No (%)†*	*Mortality No (%)†*
Gall stone	12 (10)	9 (75)	8 (67)	1 (8)
Idiopathic	7 (17)	4 (42)	7 (100)	5 (71)‡
Alcohol	4 (4)	2 (50)	3 (75)	1 (25)
Post-ERCP	2 (18)	2 (100)	2 (100)	2 (100)‡
After operation	2 (67)	0 (0)	2 (100)	1 (50)
Pancreatic cancer	1 (20)	0 (0)	0 (0)	0 (0)
Immunosuppressant therapy	1 (100)	1 (100)	1 (100)	0 (0)
Total	29	18	23	10

*Represents the percentage requiring necrosectomy within each aetiological group overall.
†Represents the percentage undergoing necrosectomy positive within each aetiological group.
‡p=0·019 Fisher's exact test. MOF=multiple organ failure.

than those of the Goris multiple organ failure score. The Goris multiple organ failure score is also a valuable predictor of prognosis; in our series only five of 15 patients with a score greater than 4 survived.

The group of patients with pancreatitis who place the greatest load on both staff and resources are those who develop pancreatic and peripancreatic necrosis.[22] In the 36 patients with necrosis in this study, the median hospital stay was 68 days with the longest stay being 300 days. Twenty nine (72%) of these patients required necrosectomy with a mortality in this series of 34%, a figure within the range 21 to 47%[23] reported from many centres but well above the rate reported by Beger and colleagues from Ulm.[11] The death rate of only 8% in the Ulm series is exceptional, and it is of interest that necrosectomy was performed in 85% of the patients identified as harbouring pancreatic necrosis.[11] Deciding the timing of necrosectomy can be difficult but is based on clinical evidence of severe disease (such as sepsis or increasing multiple organ failure), which fails to improve despite maximum intensive treatment, and on computed tomography evaluation of the location and extent of the necrosis. The median time to surgery reported by Beger *et al*[11] was seven days. In our experience, however, early surgery carries a risk of significant haemorrhage from the pancreatic bed, which can be difficult to control, given that endarteritis obliterans is incomplete and that the delineation between viable and non-viable tissue may not be clear cut. All five patients who underwent necrosectomy within two weeks of diagnosis in this series died, and significant intraoperative and postoperative haemorrhage contributed to the demise in three cases. In contrast, there were five (21%) deaths in 24 patients where necrosectomy was performed after two weeks; postoperative haemorrhage was seen in only one of these patients and was successfully controlled by a second laparotomy. In a series from Paris,[24] all 12 patients undergoing pancreatic debridement within the first eight days of admission died, whereas there were only three (27%) deaths when surgery was performed after this period. While organ failure is clearly related to mortality[25] and the median modified Goris multiple organ failure score was lower in survivors in this study, there was no difference in median score between those who died after early compared with late necrosectomy. The reoperation rate in Beger's review[11] was 27% compared with 17% in this study, and it is conceivable that reoperation may be more likely if early surgery is undertaken.

Bacterial contamination of necrosis is deemed to be a serious event.[26] It occurs in 40–70% of patients[27] and is generally associated with increased mortality; Beger and coworkers[28] found a fourfold increase in mortality (37·8% *v* 8·7%) in patients with infected necrosis. Although 47% of patients with necrosis had positive bacteriology in this study, this did not seem to influence mortality and the reasons for this discrepancy are uncertain.

Patients with severe acute pancreatitis commonly require nutritional support, including total parenteral nutrition, because of factors such as duodenal ileus and a desire to promote pancreatic 'rest'. Catheter sepsis was a significant source of morbidity in the early part of this study (Table IV), and it is now our practice to insert dedicated single lumen feeding lines when total parenteral nutrition is deemed necessary. Since the introduction of this policy, there have been no line infections in our last 31 consecutive patients. It has also become our practice to insert a feeding jejunostomy in all patients undergoing surgery so that enteral nutrition may be provided as an alternative means of nutritional support.

Morbidity in patients with pancreatitis remains significant and 35% of our directly admitted patients and 75% of our transferred patients suffered one or more complications that necessitated therapeutic intervention. Local pancreatic complications were seen in 19% of the patients admitted directly to the unit. Comparison with other published reports is difficult because of variation in criteria used, but a local complication rate of 15% seems representative.[27] Infective complications, both in the region of the pancreas and at distant sites, were the commonest reason for therapeutic intervention. Chest infection occurred in 35 patients (Table IV) and was related to surgery in 19 (54%) cases. Prophylactic antibiotic therapy has been advocated to reduce the risk of infective complications but a recent trial has suggested that while the broad spectrum antibiotic, imipenim, reduced the rate of infection in pancreatic necrosis, mortality was not improved.[29] Although subcutaneous heparin was given routinely to our patients as prophylaxis against deep venous thrombosis, such thrombosis was diagnosed in three patients and non-fatal pulmonary embolus developed in two of these patients. The superior vena cava thrombosis in one patient occurred in the presence of central line sepsis.

In conclusion, the mortality of 1·9% for patients with acute pancreatitis who were admitted directly to our unit has to be balanced against a 10-fold higher mortality in patients transferred from other units and hospitals for specialist care. Our study confirms that death rates are higher in the elderly, those with idiopathic disease, and patients with post-ERCP pancreatitis. Patients transferred from other units had lower death rates if transfer was effected within a week of

diagnosis, but further study will be needed to discover if this is a function of patient selection. Patients requiring necrosectomy remain a high risk group and mortality in our experience was prohibitively high if necrosectomy was attempted in the early period following diagnosis.

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