Fatal acute pancreatitis

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SUMMARY Review of all deaths from acute pancreatitis recorded at Glasgow Royal Infirmary between 1974 and 1984 identified 126 patients, 53 (42%) of whom had pancreatitis first diagnosed at necropsy. Aetiologies of the fatal attacks of pancreatitis included gall stones (30%), alcohol (15%), other identified aetiological factors (17%), and was unknown (38%). Overall mortality fell from 14·9% in the early half of the study to 10·8% in the latter half although in the 73 patients in whom the diagnosis of acute pancreatitis was made during life, the mortality rate was unchanged throughout. Within the group of 73 patients diagnosed during life deaths from gall stone pancreatitis have fallen by almost 50% suggesting that improved treatment of this subgroup may have occurred. The findings of this study lend support to the concept of early, complete clearance of calculi from the biliary tree, either by an endoscopic or surgical approach.

In a mainly retrospective review of acute pancreatitis from Glasgow Royal Infirmary over the decade to 1970, Imrie reported an overall mortality rate of 21·4%.1 A recent review from Bristol of the decade to 1979 found a mortality rate of 19·6%,2 a figure little changed from that of the preceding two decades.3 In prospective therapeutic trials in Glasgow, mortality from acute pancreatitis fell from 11·5% in 1971–2 to 8·7% in 1974–7.4 Such prospective trials, however, give an incomplete picture of the true incidence and mortality of acute pancreatitis by excluding patients who present atypically and those not diagnosed in life. The past decade has seen many changes in the management of acute pancreatitis and its complications but it is unclear whether these have influenced overall mortality. We have therefore undertaken a review of all deaths from acute pancreatitis at Glasgow Royal Infirmary between 1974 and 1984, during which time a series of prospective therapeutic trials were being conducted.

Methods

Patients

Patients admitted into the acute surgical receiving wards of Glasgow Royal Infirmary with a diagnosis of acute pancreatitis have been documented prospectively since 1971. Between the 1 January 1974 and the 31 December 1984 we documented 817 such patients, many of whom have been the subject of prospective therapeutic trials.5 A fatal outcome was recorded in 73 (9%) of these patients. Examination of the Hospital Activity Analysis (ICD Code 577.0) for these years revealed that a total of 975 patients with a recorded diagnosis of acute pancreatitis had been treated over this time, including 53 patients who were first diagnosed at necropsy. The 73 deaths documented prospectively and the 53 patients first diagnosed at necropsy give a total of 126 deaths for an overall mortality rate of 12·9%. The diagnosis in these 126 patients was confirmed at post mortem examination in 99 (79%), laparotomy in 10 (8%) and in the remainder on a clinical presentation and course of illness consistent with the diagnosis of acute pancreatitis and a serum amylase above 1200 IU/l (normal range 70–300 IU/l).

AetiologY of acute pancreatitis

Gall stones were considered to be the underlying cause of acute pancreatitis when they were recovered at necropsy or laparotomy, and in two patients on radiological evidence (intravenous cholangiography – one, plain x-ray – one). Alcohol was incriminated in patients admitting to, or suspected of drinking an excessive amount.6 Patients with other recognised causes of acute pancreatitis have been studied as a group (see below) as have those in whom no definite aetiological factor could be implicated. Table 1 details the age and sex of the groups and the proportion first diagnosed at necropsy.
Fatal acute pancreatitis

Table 1  
Aetiology of fatal acute pancreatitis in relation to patient age and sex and proportion of patients first diagnosed at necropsy

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>n</th>
<th>Male:Female</th>
<th>Mean age necropsy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gall stones</td>
<td>39</td>
<td>19:20</td>
<td>68</td>
</tr>
<tr>
<td>Alcohol</td>
<td>20</td>
<td>16:4</td>
<td>48</td>
</tr>
<tr>
<td>Other causes</td>
<td>23</td>
<td>12:11</td>
<td>62</td>
</tr>
<tr>
<td>Unknown causes</td>
<td>50</td>
<td>21:29</td>
<td>66</td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>68:64</td>
<td>63</td>
</tr>
</tbody>
</table>

*Six patients with >1 aetiological factor.

Pancreatic morphology was classified according to the description of the organ at laparotomy or necropsy supplemented by histological data where available. Pancreatic pseudocyst and abscess were defined respectively as a pancreatic or peripancreatic collection of fluid or pus. Black pancreatic and peripancreatic tissue either apparent superficially or on sectioning of the gland was diagnosed as necrosis but included in this group were patients with extensive panlobular parenchymal destruction on microscopy. The remaining patients with less severe parenchymal destruction were labelled as having had acute haemorrhagic pancreatitis when haemorrhage was apparent on the surface, or on sectioning of the gland, and as having had acute interstitial pancreatitis when the pancreas was inflamed with only fat necrosis and focal parenchymal necrosis on histology.

Analysis of deaths

Death was categorised as ‘pancreatic’ when it appeared to have been a direct consequence of acute pancreatitis and this included some patients in whom events such as myocardial infarction or pulmonary embolism complicated severe acute pancreatitis. Where death appeared to be a consequence of another unrelated medical condition – for example, liver failure or hypothermia, or where pre-existent medical disease was a major contributing factor to death – for example, ischaemic heart disease, carcinoma or chronic obstructive airways disease, such deaths were categorised as ‘medical’. Early deaths were defined as those occurring within seven days of admission and late deaths, as those occurring after this time.

Statistical analysis

Statistical analysis was conducted by Fisher's exact test and by the Student's t-test.

Results

The annual incidence and mortality of acute pancreatitis and the number of patients first diagnosed at necropsy is shown in Figure 1. Mortality is seen to decrease throughout the 11 year period. The overall mortality rate for the first half of the study (1 January 1974 to the 30 June 1979) was 14.9% compared with 10.8% for the latter half. The mortality rates for the 73 patients documented prospectively were 8.9% and 9% respectively and the fall in overall mortality is explained by a reduction in the number of patients who were first diagnosed at necropsy, 38 (72%) of whom were recorded in the first half of the study.

Sixty-eight (93%) of the 73 patients documented prospectively were first diagnosed on clinical and biochemical grounds and the remainder at laparotomy. Of the 53 patients first diagnosed at necropsy 36 (68%) had presented atypically with known or suspected medical conditions, 32 (60%) of them to physicians rather than surgeons. No particular clinical syndrome emerged as being most commonly associated with undiagnosed pancreatitis but rather these patients had widely varying presentations which suggested neurological disease in six, respiratory disease in six, and cardiac failure, liver failure, and ketoacidosis each in five patients. In 10 (19%) of these undiagnosed patients, pancreatitis was an unsuspected cause of postoperative deterioration (see below). Only seven (13%) of these 53 patients had presented with abdominal pain and a serum amylase level had been measured in only five.

Fig. 1  
Annual incidence and mortality of acute pancreatitis and numbers first diagnosed at necropsy.
Pancreatitis 2(9%)

Biliary laparotomy or pancreatitis.

Table 2 Relationship between pancreatic morphology at laparotomy or necropsy and the distribution of gall stones in the biliary tree in the 39 patients with fatal gall stone pancreatitis

<table>
<thead>
<tr>
<th>Pancreatic morphology</th>
<th>Ductal calculi (n=23)</th>
<th>Calculi in gall bladder only (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial pancreatitis</td>
<td>4(17%)</td>
<td>4(25%)</td>
</tr>
<tr>
<td>Haemorrhagic pancreatitis</td>
<td>2(9%)</td>
<td>3(19%)</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
<td>7(30%)</td>
<td>3(19%)</td>
</tr>
<tr>
<td>Pancreatic abscess</td>
<td>8(35%)</td>
<td>3(19%)</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>1(4%)</td>
<td>2(12%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1(4%)</td>
<td>1(6%)</td>
</tr>
</tbody>
</table>

No significant difference between groups (Fisher’s exact test).

Table 3 Incidence of abscess and necrosis within each aetiological group in patients first diagnosed in life and at necropsy

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Diagnosed in life</th>
<th>Diagnosed at post mortem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Necrosis</td>
<td>Abscess</td>
</tr>
<tr>
<td>Gall stones</td>
<td>7(27%)</td>
<td>9(35%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>6(50%)</td>
<td>2(17%)</td>
</tr>
<tr>
<td>Other</td>
<td>1(17%)</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>4(14%)</td>
<td>3(10%)</td>
</tr>
</tbody>
</table>

(9%) of them. The majority of the patients dying from acute pancreatitis had presented directly to the medical and surgical units of this hospital, only seven patients (6%) being secondary referrals from other hospitals.

GALL STONE PANCREATITIS

Thirty nine patients (30%) had acute pancreatitis associated with the presence of gall stones. Six patients also had other potential aetiological factors, namely alcohol abuse (three), recent cardiopulmonary bypass (one), biliary surgery (one), and hypothermia (one). Figure 2 shows the distribution of gall stones in the biliary tree and Table 2 the relationship between the distribution of gall stones and the pancreatic morphology found at laparotomy or post mortem examination. Severe pancreatic destruction (abscess or necrosis) was present in 21 patients (54%) and was found more commonly in the 23 patients (59%) with calculi in the extrahepatic ducts than in the remainder in whom calculi were confined to the gall bladder. Table 3 details the 21 patients with severe pancreatic destruction, 16 (76%) of whom were diagnosed in life. Gall stones impacted at the ampulla of Vater were found in only two patients (both elderly women). Both died of septicaemia associated with severe cholangitis as did one other patient with gall stones throughout the biliary tree.

Nine patients (23%) had experienced previous attacks of acute pancreatitis. Seven presented in the early half of the study, three having been discharged only six, seven, and 12 days before their final fatal attack. Two patients who had previously undergone cholecystectomy developed recurrent acute pancreatitis in association with persistent or recurrent calculi.

ALCOHOL ASSOCIATED PANCREATITIS

Twenty patients had a history of chronic alcohol abuse. Three of these patients (mentioned above) had gall stones. Sixteen (80%) were men and patients with alcohol associated acute pancreatitis were significantly younger than those with acute pancreatitis attributable to other causes (mean age 47.9 years v 66.1 years, p<0.001). Eleven patients (55%) had severe pancreatic destruction (Table 3). Seven patients had alcoholic liver disease consisting of cirrhosis in five and acute alcoholic hepatitis in two; four died in frank hepatic failure. Five patients (25%) had a history of previous pancreatitis, three of whom had required surgery (pseudocyst drainage – two, abscess drainage – one).

OTHER IDENTIFIED AETIOLOGICAL FACTORS

Twenty three patients had other recognised aetio-
Fatal acute pancreatitis

Table 4  Surgical treatment of patients with fatal acute pancreatitis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>M-F</th>
<th>Mean age (yrs)</th>
<th>Gallstone (%)</th>
<th>Admission (days)*</th>
<th>Further procedures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>4</td>
<td>3:1</td>
<td>53</td>
<td>25%</td>
<td>6(2–19)</td>
<td>25%</td>
</tr>
<tr>
<td>Necrosectomy</td>
<td>3</td>
<td>1:2</td>
<td>55</td>
<td>100%</td>
<td>12(1–14)</td>
<td>100%</td>
</tr>
<tr>
<td>Abscess</td>
<td>7</td>
<td>3:4</td>
<td>63</td>
<td>57%</td>
<td>22(3–36)</td>
<td>29%</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>7</td>
<td>7:0</td>
<td>58</td>
<td>43%</td>
<td>47(8–90)</td>
<td>43%</td>
</tr>
<tr>
<td>Various</td>
<td>2</td>
<td>1:1</td>
<td>43</td>
<td>50%</td>
<td>(1,6)</td>
<td>50%</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>15:8</td>
<td>57</td>
<td>57%</td>
<td></td>
<td>43%</td>
</tr>
</tbody>
</table>

*Median (range).

logical factors implicated. Four patients had hypothermia, all of whom were elderly (mean age 90 years) and three of whom were women. One had gall stones and acute pancreatitis may have preceded the hypothermia. Eight patients developed acute pancreatitis after upper abdominal surgery. Three had undergone gastrectomy (two with splenectomy), two had undergone splenectomy, and three had undergone biliary or pancreatic surgery. Three patients developed acute pancreatitis after cardiopulmonary bypass and two after translumbar aortography. Only one of the patients with postoperative pancreatitis was diagnosed in life having been re-explored for suspected anastomotic leakage after gastrectomy.

Four patients had acute pancreatitis in association with pancreatic carcinoma (primary pancreatic – three, metastatic from bronchus – one). Two other patients developed acute pancreatitis associated with fulminant viral hepatitis and iatrogenic intravascular haemolysis respectively. Eleven patients (48%) had severe pancreatic destruction (Table 3) and only three patients (those having undergone biliary or pancreatic surgery) had a history of previous attacks.

**UNKNOWN AETIOLOGY**

The 50 patients (38%) in whom no definite aetiological factor could be implicated (despite laparotomy or post mortem examination in all but 13) comprise the largest single group. Possible aetiologies were thought to include ischaemia/hypotension in six, septicaemia in three, and steroid therapy in two. Only 13 (26%) had severe pancreatic destruction (Table 3) and none had a history of previous attacks of acute pancreatitis.

**SURGERY**

Surgery for complications was performed in 23 patients (18%) during their final illness, 10 requiring multiple operations (Table 4). Six of the seven patients having surgery for abscess had a post mortem examination and five were found to have residual abscess and/or necrosis. Thirteen patients having surgery had gall stones. In six of these patients gall stones were not eradicated at surgery. In four patients gall stones were not identified at surgery, despite multiple operations in two of these patients. Only one of these patients had been treated during the latter half of the study.

**ANALYSIS OF DEATHS**

Early 'pancreatic' deaths were often associated with fulminant acute pancreatitis. Such deaths were most commonly seen in older patients with no identifiable aetiological factors but were also common in younger patients in whom alcohol was implicated (Fig. 3). Late 'pancreatic' deaths, usually caused by abscess and/or necrosis with sepsis and multiorgan failure, were most common in patients with a gall stone aetiology. Early and late 'medical' deaths were most often seen in patients with acute pancreatitis as a result of other identified aetiological factors. Significant underlying medical disease was present in 71% and 86% of the early and late 'medical' deaths compared with only 46% and 42% of the early and late 'pancreatic' deaths respectively. Overall 56% of the deaths were considered directly attributable to acute pancreatitis and 32% to 'medical' causes. In 17 patients (13%) there were no laparotomy or post mortem data. Of the 73 patients diagnosed in life, 60% died of 'pancreatic' causes and 16% of 'medical' causes compared with 49% and 51% respectively of those first diagnosed at necropsy.

**Discussion**

Throughout the 11 year period reviewed the numbers of patients treated for acute pancreatitis each year
has remained relatively constant. Given the 23\% reduction in our hospital district catchment population that has occurred over this time, the local incidence of acute pancreatitis has probably risen and this would be in agreement with reports from elsewhere in the UK.\textsuperscript{23,100} Whether this reflects a real increase in the local incidence of acute pancreatitis or whether more patients are being diagnosed because of increased investigative zeal is unknown. Interest in acute pancreatitis at this hospital predated the period of the current study by several years, these patients having been actively sought and documented prospectively since 1971.\textsuperscript{4} A real increase in the local incidence is therefore thought the more likely explanation.

Overall mortality has fallen reflecting a reduction in the numbers of patients first diagnosed at necropsy and this may be partly explained by a concomitant drop in the hospital’s post mortem examination rate. The proportion of pancreatitis deaths that were undiagnosed before necropsy fell from 51\% in the first part of the study to 29\%, a fall of 43\%. During these periods the hospital’s necropsy rate has fallen from 29\% of all deaths in the first part of the study to 20\% of all deaths latterly, a fall of 31\%.

Our incidence figures and mortality rates obviously fail to take account of all patients with acute pancreatitis who are undiagnosed in life. Although presumably only a proportion of such patients die, improvements in diagnosis leading to increased numbers being diagnosed in life might contribute to a reduction in the numbers of patients first diagnosed at post mortem examination.

It is disappointing that the mortality of patients diagnosed in life and documented prospectively has remained unchanged at around 9\%. Deaths from gall stone pancreatitis in patients studied prospectively have, however, fallen by 47\% from 17 in the first half of the study to nine. This is partly because of a reduction in the number of fatal recurrent attacks (seven v only two in the latter half of the study) and particularly to the abolition of early fatal recurrence. Elimination of these deaths argues in favour of the policy of early cholecystectomy for gall stone pancreatitis which we\textsuperscript{1} and others have favoured,\textsuperscript{13-14} rather than readmitting these patients for surgery six to 12 weeks after their original attack. The fall in the number of deaths attributed to gall stone pancreatitis may also be because of the more successful eradication of gall stones at operation in the latter half of the study. The aim of surgery for gall stone pancreatitis is clearance of all calculi from the biliary tree. In the early years of the study this aim was clearly not achieved. Failure to eradicate gall stones was because cholecystostomy was done without operative cholangiography in one case and to a choledochoduodenostomy being done in another after failure of supraduodenal exploration. In four other patients gall stones were not identified at operation (abscess drainage – two, pseudocyst drainage – one, and laparotomy for haemorrhage – one). Gall stones giving rise to acute pancreatitis are often small, can be difficult to diagnose by standard imaging techniques, and as shown here, may be overlooked at laparotomy. Finally the fall in the number of deaths associated with gall stone pancreatitis may also reflect a decrease in the incidence of this diagnosis in our practice, for reasons which are not clear. In the early years of this study gall stones accounted for 52\% of first attacks of primary acute pancreatitis.\textsuperscript{5} Since 1979 gall stones have been incriminated in only 41\% of first attacks whereas the incidence of attacks of unknown aetiology has increased from 13\% to 22\%.\textsuperscript{5}

The continued presence of calculi in the extrahepatic ducts appears to be associated with more severe pancreatic destruction (abscess or necrosis) than when gall stones were confined to the gall bladder at the time of laparotomy or necropsy. It is conceivable that earlier clearance of these calculi by operation or endoscopic sphincterotomy would have favourably altered the outcome in some of these patients. Immediate operation to clear obstructing gall stones from the ampulla and biliary tree before irreversible pancreatic necrosis develops has been proposed by Acosta and coworkers.\textsuperscript{12} This approach, although supported by Stone,\textsuperscript{11} has not gained favour and an increased mortality has been reported in association with immediate operation.\textsuperscript{12-13} The advanced age of the patients subsequently dying of gall stone pancreatitis (mean age 68 years) also militates against a policy of immediate surgery, although it may be tolerated by younger patients. Endoscopic sphincterotomy appears to be a safe alternative in this situation\textsuperscript{16} and may well be beneficial\textsuperscript{16} although its application in fulminant cases awaits full evaluation.

Five (25\%) of the patients with alcohol associated acute pancreatitis had liver cirrhosis, a similar incidence to a large American series where alcohol was a much commoner cause of acute pancreatitis, accounting for 68\% of patients overall.\textsuperscript{16}

Acute pancreatitis caused by other identified aetiologies was infrequently diagnosed before necropsy, particularly pancreatitis developing postoperatively. It is likely that diagnosis of these patients in life would have altered management and perhaps the outcome in some. In 1978 we recommended better surveillance of patients undergoing ‘at risk’ procedures\textsuperscript{20} and only two deaths from postoperative pancreatitis were recorded in the latter half of the study. Surveillance nowadays might most easily be
Fatal acute pancreatitis was thought to explain the acute pancreatitis in at least some of the patients in whom no other aetiological factor could be identified. This was the largest group of patients and the high percentage with an unidentified aetiology is surprising, although similar to the recent Bristol experience. Attention has often focussed in the past on a comparison of outcome in gall stone and alcohol associated acute pancreatitis while the idiopathic aetiological group is regularly shown to have the highest mortality. Improved identification of aetiology during life and at necropsy is desirable. Faecal sieving and ERCP will increase the detection of gall stones and routine viral screening or blood alcohol concentrations on admission might improve the diagnostic rate further. There is also need for a meticulous post mortem examination protocol to avoid overlooking small calculi in the common bile duct or ampulla and rarer associations such as parathyroid adenomas.

Death was considered to be due to ‘medical’ causes in 51% of the 53 patients first diagnosed at necropsy. In a retrospective study such as this it can be difficult to determine the actual contribution of the acute pancreatitis to the patient’s death and in some it is possible that pancreatitis may have occurred as a result of terminal organ failure. In only seven patients (13%) was the pancreatitis mild on the pathologist’s assessment and considered to be an incidental finding at post mortem. In the remainder pancreatitis was considered to be either the major factor or a significant additional factor contributing to death and in the majority of these patients pancreatitis was thought to account for the patients’ presenting symptoms.

The preponderance of ‘pancreatic’ deaths amongst the patients diagnosed in life, particularly in those with a gall stone or alcohol aetiology, suggests scope for further improvement in surgical management. The limitations of the traditional surgical approaches for the management of pancreatic necrosis or abscess are, however, highlighted by the frequent need for reoperation and the incidence of residual abscess and/or necrosis at necropsy. Newer developments in imaging techniques and the promising preliminary results of the recently described techniques of post-operative lavage or open packing after digital debridement and necrosectomy for pancreatic necrosis or abscess await full evaluation. A proportion of patients may benefit, but a dramatic overall improvement in the mortality rate is unlikely to follow. One third of the patients reported here died of medical causes and it was considered that surgical treatment had little or nothing to offer them. Other patients who might benefit from surgery were usually old or had concurrent medical disease and such patients often do poorly after surgery even with intensive care therapy. The nihilistic attitude has not much to commend it but a realisation of the task ahead is sensible. More careful surveillance in diagnostic terms and the application of early ERCP and endoscopic sphincterotomy in gall stone pancreatitis as well as a vigorous surgical policy to infected necrotizing pancreatitis must be the way ahead.

References