Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis

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Acute pancreatitis is a disease with a very varied outcome, ranging from complete resolution to death. Overall, the mortality rate in the UK is 7.5–9%; in patients with predicted severe disease, the mortality rate ranges from 14% to 30%, depending on the criteria for prediction, and in patients with complications (severe acute pancreatitis, as defined in the Atlanta criteria) the mortality rate is 25–30%. Approximately one third to half the deaths in acute pancreatitis occur during the first week, as a result of progressive organ failure (multiple organ dysfunction syndrome (MODS)). Late deaths occurring more than one week after admission to hospital are often associated with local complications, such as infected pancreatic necrosis, and these patients also usually show features of sepsis and MODS.

In the past, patients with acute pancreatitis have been categorised according to the presence or absence of complications, as the definition of severe disease. This was codified in the Atlanta criteria which define severe pancreatitis as the presence of any complication. These complications include systemic organ failures, as well as local manifestations. However, clinical experience is that many patients with early organ failure respond rapidly to treatment and appear to have an otherwise uncomplicated outcome. Recently, it has been shown that organ failure in the first week of admission is a dynamic process and that progression of early organ failure was attended by a mortality rate in excess of 50%.

The present study was conducted using a large database of patients with predicted severe acute pancreatitis. The aim was to categorise patients as having transient or persistent organ failure in the first week of acute pancreatitis, to investigate the relationship of these categories with fatal outcome, and to determine the relationship of persistent organ failure with subsequent development of local complications.

METHOD
This study reviews a database of patients with predicted severe acute pancreatitis entered into a placebo controlled trial of lexipafant. The database contained 290 patients with a confirmed diagnosis of acute pancreatitis, aged over 18 and less than 80 years, with an APACHE-II score >6 in the 24 hours before entry to the study. All patients were primary admissions to hospital and had symptoms for less than 72 hours before entry to the study. Patients were recruited from 78 hospitals, including 18 centres constituting the British Acute Pancreatitis Study Group. All data were recorded prospectively. Patients received an infusion of either lexipafant or placebo for up to seven days and were followed until hospital discharge or death. The management of these patients was otherwise according to the usual practice of the responsible clinician.

The variables recorded in the study proformas included the presence and severity of organ failure on every day during the first week, subsequent local complications, subsequent episodes of sepsis, and death during the same hospital admission. Death at a later time during the trial was also recorded if notified to the researcher. The electronic database is no longer accessible to the investigators because it was held by a company that is no longer trading: this study was conducted by the manual inspection of the full version of the trial report prepared by the trial sponsor (British Biotech Plc) and provided to each member of the study group.

Definition of organ failure
Organ failure was defined as in the previous report, using the Marshall score, which approximates very closely to the definitions used in the Atlanta criteria. Organ failure scores were

Abbreviations: MODS, multiple organ dysfunction syndrome; CT, computed tomography
were recorded each day during the first week for all organ systems (with the exception of the hepatic score which was excluded to avoid confounding by the effects of gall stones and obstructive jaundice). A score of 2 or greater for any one organ system equates to organ failure and was achieved when the following cut-offs were exceeded: cardiovascular failure if systolic blood pressure was $<90$ mm Hg despite fluid replacement; respiratory failure if the PaO$_2$/FiO$_2$ ratio was $<300$ mm Hg; central nervous system failure if the Glasgow coma score was $<13$; coagulopathy if the platelet count was $<80 \times 10^9$/l; and renal failure if plasma creatinine was $>170$ mmol/l. If any of these criteria were met, the patient was recorded as having organ failure on that day. Transient organ failure was defined as organ failure present on less than three consecutive days excluding day 0, and persistent organ failure was recorded when organ failure was present on three or more days after day 0, where day 0 was the day of entry to the study and day 1 was the 24 hour period starting at 8.00am on the day after entry.

Records were inspected to determine the presence of absence of organ failure on each day of the first week of study and whether this organ failure was persistent (≥48 hours) or transient (<48 hours). Cross tabulations were made with outcome, in particular with death and local complications. Also, records of all serious adverse events reported in the trial were inspected to gain information about complications of acute pancreatitis.

Where appropriate, differences in distribution were tested with the $\chi^2$ test or Fisher’s exact test. Significance was accepted at the 5% level.

**RESULTS**

The database contained information on 290 patients of whom 40 died. Table 1 shows that a fatal outcome was almost always associated with an APACHE-II score of $>8$. Only two patients with initial APACHE-II scores of 7 and 8 died, one within 24 hours from rapidly progressive organ failure and one on day 42 from pancreatic necrosis. Patients with an APACHE-II score $>8$ on admission had an 18% mortality rate.

Of the 40 deaths, 15 occurred within the first week. All of these patients had organ failure from the day of admission until the day of death. Twenty-five patients died more than one week (median 20.5 days (range 8–132)) after admission. Three late deaths at 114, 115, and 169 days were found not to be due to acute pancreatitis; the remaining 37 deaths were ascribed to complications of acute pancreatitis.

The relationship between the presence and duration of organ failure within the first week of study and subsequent death is shown in table 2. Persistent organ failure, whether present at admission or arising during the first week, was significantly associated with a fatal outcome. Of the 40 patients who died, three had no organ failure in the first week, 12 had single organ failure, and 26 had two or more early organ failures (table 3). All patients with multiple organ failures had pulmonary or renal insufficiency. Of the three patients without organ failure during the first week who subsequently died, one developed continuing signs of sepsis with abdominal discomfort and died from presumed infected pancreatic necrosis on the 25th day. Two others died of unrelated causes (brain stem stroke at 144 days and myocardial infarction on day 5, no autopsy evidence of pancreatitis). One patient died after early organ failure that resolved within less than 48 hours. After a prolonged hospital stay, he developed pancreatic necrosis; necrosectomy was performed but his condition deteriorated and he died after 81 days from sepsis and acute renal failure.

As noted previously, 44% of patients already had organ failure at entry to the study. In the present analysis, organ failure was present in 148 (51%) patients in the first 24 hours of the study (that is, on day 0 (study entry) or day 1). Of 174 patients who developed organ failure at entry or within the first week of the study, 71 (41%) had transient organ failure that resolved in 48 hours or less. Of these patients only one died, from the effects of pancreatic necrosis. The types of organ failure present in patients with transient organ failure are shown in table 4. Of the 103 patients with persistent organ failure, 36 (35%) died, of whom 14 died within the first week from progressive organ failure.

Of 174 patients with organ failure during the first week of the study, 59 later developed local complications. In contrast, only 12 patients developed symptomatic local complications in the absence of early organ failure. Detailed analysis of the whole group was not possible because the trial protocol did not include a confirmatory diagnosis of complications.
Table 5  Relationship between duration of organ failure and development of local complications in 110 patients with record of a serious adverse event

<table>
<thead>
<tr>
<th></th>
<th>Local complications</th>
<th>No local complications</th>
<th>No data*</th>
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<tbody>
<tr>
<td>Persistent organ failure</td>
<td>52</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Transient organ failure</td>
<td>27</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>No organ failure</td>
<td>31</td>
<td>2</td>
<td>27</td>
</tr>
</tbody>
</table>

*No data from 14 patients that died in the first week and eight survivors with inadequate records to assess local complications. Local complications were necrosis or pseudocyst; early fluid collections were not considered as complications.

Significant association of persistent organ failure and local complications: $\chi^2 = 24.23; df = 2; p < 0.001$

Although the observation that approximately half the patients with a raised APACHE-II score had organ failure in the first day or two of hospital admission limits the usefulness of systemic organ failure as a marker of response to treatment in randomised trials, it has been suggested that the progress of the organ failure itself could be a useful marker of disease severity. Butler and colleagues also used a cut off APACHE-II score >6 to predict severity and found that deterioration of organ failure was associated with a mortality rate greater than 50%. They did not comment on the duration of early organ failure.

The present study clarifies the relationship between the dynamic nature of organ failure and subsequent death. Our data show that patients with organ failure which resolved within 48 hours have a very low risk of death, whereas organ failure which persists for longer than this time, even if not initially progressive, carries a grave prognosis.

The relationship between duration of organ failure and risk of death was similar, irrespective of the time of onset of organ failure. Although most patients who developed organ failure had done so at the time of study entry or shortly thereafter, 22 patients (7.5%) developed new organ failure after the first 24 hours of the study. Of these, half had transient organ failure with no deaths and half ($n = 11$) had persistent organ failure with four deaths. There was no difference in mortality rate between initial organ failure and new organ failure developing within the first week, suggesting that the important determinant of risk of death is the persistence of organ failure for more than 48 hours.

This analysis shows for the first time that persistence of organ failure during the first week is strongly associated with subsequent development of local complications. This is unsurprising given the association we observed of persistent organ failure with late deaths and the fact that most late deaths are associated with the presence of local complications. It suggests that the presence of extensive necrosis during the first week of the illness may be a factor in the persistence of organ failure but it does not exclude the opposite relationship as it is possible that persistent organ failure with associated poor oxygenation and reduced perfusion of the inflamed pancreas may contribute to extension of necrosis. The relationship between organ failure, necrosis, and fatal outcome is not well understood: Le Mee and colleagues found a high mortality rate in infected necrosis, associated with multiple (three or more) organ failure; some authors found no correlation of organ failure with the extent of pancreatic necrosis or the presence of infection; and in contrast, Lankisch and colleagues and Isenman and colleagues found organ failure more commonly in the presence of infection but in their patients the extent of necrosis was related to organ failure only in sterile necrosis. Lankisch and colleagues pointed out that initial organ failure and (more severe) late organ failure were both more common in patients with pancreatic necrosis but that both initial and late organ failure, and pancreatic necrosis, could occur independently in many patients. The present data suggest that persistent organ failure during the first week of admission is a marker of increased risk of pancreatic necrosis, as manifest in local complications, but the data do not clarify whether the association depends on multiple (three or more) organ failure or organ failure contributing to the incidence and extent of pancreatic necrosis.

In this study there was no systematic search for local complications. CT was not employed routinely during the first week of the illness, nor was a follow up CT scan required by the trial protocol. Consequently, there may be some underreporting of local complications. However, all patients were followed until discharge from hospital, and any patient readmitted with a pancreatitis related problem was
documented. Therefore, we are confident that the large majority of symptomatic local complications have been recorded. It can be argued that asymptomatic areas of necrosis are not clinically significant. In the subgroup of patients with documented serious adverse events, there was a clear relationship between persistence of early organ failure and late development of local complications (table 5). This study suggests that persistent organ failure in the first week could be a useful marker for the subsequent development of symptomatic local complications.

We have not commented on the severity of organ failure, which has been shown by others to be associated with local complications. Instead, we chose to apply the Atlanta criteria which depend on whether the threshold for organ failure has been passed. Transient organ failure was associated with a good outcome; most of these patients had single organ failure. However, persistent organ failure identifies patients at increased risk of death, and although most patients who died had multiple organ failure in the first week of their illness, late death was associated in more than 25% of cases with persistent single organ failure during the first week.

Patients with transient organ failure almost always had single organ failure, usually pulmonary. Only four patients with transient organ failure had two organ failures. This is further supporting evidence that transient organ failure is associated with less severe disease as the incidence of multiple organ failure is much lower than in patients with persistent organ failure.

This analysis cannot shed light on whether the dynamic nature of organ failure can be modified with a beneficial effect on outcome. We have observed a marker of poor outcome (persistent organ failure). It is tempting to speculate that efforts to ameliorate organ failure early in the course of acute pancreatitis might improve outcome. If the persistence of organ failure leads to systemic hypoxia, and perhaps reduced perfusion, that could be a mechanism to cause or extend areas of necrosis in the pancreas. In that case, early aggressive circulatory support with intravenous fluids and inotropes if necessary, and oxygen supplementation, might lead to improved pancreatic perfusion and a reduced risk of necrosis and subsequently death. Experimental evidence suggests that disturbance of the microcirculation may contribute to the development of pancreatic necrosis. There is some clinical evidence that early aggressive resuscitation may improve outcome which lends support to this hypothesis.

However, there is probably an irreversible minimum mortality in severe acute pancreatitis, dependent on the severity of the early organ dysfunction syndrome. A substantial minority of our patients died within the first week of the illness of rapidly progressive multiple organ failure. Until an effective mechanism is found to interrupt the downward spiral of accelerating organ failure in these patients, general supportive care is all that can be offered. Nevertheless, these findings suggest the tantalising possibility that patients with persistent early organ failure represent a group at high risk of local complications and late death in whom aggressive supportive therapy and appropriate management of pancreatic necrosis might have the potential to improve outcome.

The importance of this study to our understanding of the pathophysiology of acute pancreatitis lies in the recognition that a single record of organ failure, as defined in the Atlanta criteria, is insufficient for the diagnosis of severe acute pancreatitis. Patients without early organ failure, or with early organ failure that resolves within 48 hours, are at very low risk of developing local complications and death. This calls into question whether such transient organ failure should be reckoned as a complication of pancreatitis and a marker of severe disease. Such patients usually respond rapidly to initial therapy and most leave the hospital within seven days.

Selection of patients for clinical trials of therapy is difficult in acute pancreatitis. Currently, APACHE-II is widely used to identify patients at high risk of complications although this system is not ideal and efforts continue to improve prediction using other features, such as obesity. As noted above, APACHE-II identifies a group of patients in which a majority already have organ failure. This is unsatisfactory if the presence of complications is used as an end point as therapy cannot influence the high pre-existing rate of organ failure. In the present study, an APACHE-II score >8 identified almost all patients who died from pancreatitis but selected a group with only half the mortality rate of that seen in patients with persistent early organ failure. If death or local complications are to be the end point of a clinical trial, persistent organ failure in the first week of hospital admission seems to be an appropriate way to select patients for study.

In conclusion, we have extended the observation of Buter and colleagues that the dynamic nature of organ failure arising during the first week of an attack of acute pancreatitis has a substantial prognostic effect. Patients with organ failure that resolves within 48 hours have a very low risk of local complications and death. In contrast, patients who have organ failure (as defined in the Atlanta criteria, equivalent to any organ score of two or more in the Marshall system) which persists for three or more days have a greater than one in three risk of fatal outcome. Local complications arise in the majority of patients with persistent organ failure. In contrast, transient organ failure has only a 25% risk of symptomatic local complications and these patients rarely die.

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APPENDIX

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REFERENCES
EDITOR’S QUIZ: GI SNAPSHOT

Painful ascites

Clinical presentation
A 67 year old woman presented initially with a history of recurrent urinary tract infections. Routine imaging with ultrasound incidentally detected a 7 cm × 8 cm well defined echogenic mass within the right lobe of the liver. Follow up with six monthly imaging was planned. Five months after initial presentation, the patient presented with abdominal distension and pain. Clinical examination revealed icterus, hepatomegaly, and ascites. Blood parameters were as follows: bilirubin 51 μmol/L, alanine aminotransferase 160 IU/L, alkaline phosphatase 294 IU/L, gamma glutamyl transferase 136 IU/L, albumin 37 mg/dL, haemoglobin 15.8 g/dL, WCC 8.6 × 10^9/L, platelets 337 × 10^9/L, prothrombin time 14.8 seconds, and α fetoprotein 3.1 IU/L. A contrast enhanced computed tomography scan showed a 8 × 7 cm mass of predominantly fatty attenuation, caudate lobe hypertrophy, and ascites. Gadolinium enhanced magnetic resonance imaging showed that the mass was composed of fat and vascular tissue.

Question
What conclusions could be drawn from this image (fig 1)?

See page 1355 for answer

This case is submitted by:

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Figure 1  Hepatic venography showing absence of flow in the hepatic veins.

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Painful ascites

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