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

C D Johnson, M Abu-Hilal, Members of the British Acute Pancreatitis Study Group

Background: In predicted severe acute pancreatitis, many patients develop organ failure and recover without local complications, and mortality is only 14–30%. It has been suggested that half of patients with progressive early organ failure may die, but there are no data to relate death or local complications to duration of early (week 1) organ failure.

Aims: To determine mortality rates in patients with transient (<48 hours) and persistent (>48 hours) early organ failure and to show whether persistent organ failure predicts death or local complications.

Patients: A total of 290 patients with predicted severe acute pancreatitis previously studied in a trial of leupafant, recruited from 78 hospitals through 18 centres in the UK.

Method: Manual review of trial database to determine: the presence of organ failure (Marshall score ≥2) on each of the first seven days in hospital, duration of organ failure, and outcome of pancreatitis (death, complications by Atlanta criteria).

Results: Early organ failure was present in 174 (60%) patients. After transient organ failure (n = 71), outcome was good: one death and 29% local complications. Persistent organ failure (n = 103) was followed by 36 deaths and 77% local complications, irrespective of onset of organ failure on admission or later during the first week.

Conclusion: Duration of organ failure during the first week of predicted severe acute pancreatitis is strongly associated with the risk of death or local complications. Resolution of organ failure within 48 hours suggests a good prognosis; persistent organ failure is a marker for subsequent death or local complications.

METHOD

This study reviews a database of patients with predicted severe acute pancreatitis entered into a placebo controlled trial of leupafant. 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 leupafant 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, 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.

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 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 or 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 PaO₂/FiO₂ ratio was <300 mm Hg; central nervous system failure if the Glasgow coma score was <13; coagulopathy if the platelet count was <80×10⁹/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 or 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 χ² 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,10 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

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Table 1 APACHE-II scores in the first 24 hours and subsequent survival in 290 patients with predicted severe acute pancreatitis

<table>
<thead>
<tr>
<th>APACHE-II score</th>
<th>Survived</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>7, 8</td>
<td>72</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>172</td>
<td>38 (18%)</td>
</tr>
<tr>
<td>Missing data</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

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Table 2 Relationship between the presence or absence, and duration of organ failure (OF) in the first week of the study, and subsequent death in 290 patients with predicted severe acute pancreatitis

<table>
<thead>
<tr>
<th></th>
<th>Survived</th>
<th>Died</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No organ failure</td>
<td>113</td>
<td>3</td>
<td>116</td>
</tr>
<tr>
<td>OF at entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>59</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>Persistent</td>
<td>56</td>
<td>32</td>
<td>88</td>
</tr>
<tr>
<td>New OF within 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Persistent</td>
<td>11</td>
<td>4</td>
<td>15</td>
</tr>
</tbody>
</table>

Significant association of death with persistent organ failure compared with transient or no organ failure: χ² = 62.54; df = 2; p < 0.001.

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Table 3 Distribution of organ failures (OF) in the first week in 40 patients with acute pancreatitis who subsequently died

<table>
<thead>
<tr>
<th>Organ failure</th>
<th>Survived</th>
<th>Died</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No organ failure</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Single OF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>10</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Renal</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Multiple OF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary and renal</td>
<td>12</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>3 or more systems</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

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Table 4 Types of organ failure recorded in 71 patients with transient (<48 hours) organ failure (OF) in the first week of study

<table>
<thead>
<tr>
<th>Organ failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>61</td>
</tr>
<tr>
<td>Renal</td>
<td>3</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>3</td>
</tr>
<tr>
<td>Multiple OF</td>
<td></td>
</tr>
<tr>
<td>Pulmonary and renal</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary and coagulopathy</td>
<td>1</td>
</tr>
</tbody>
</table>
not require routine follow up computed tomography (CT),
and confirmation of the presence or absence of local
complications was often lacking. Therefore, the relationship
between early organ failure and subsequent local complica-
tions was examined in a subgroup of patients for whom a
serious adverse event was recorded in the trial database.
In these patients (n = 110) there were 14 early deaths within
the first week. Of 36 patients who subsequently developed a
local complication, 20 died, compared with five of 52 without
documented local complications (missing data in eight
survivors). There was a significant association between
duration of early organ failure and later detection of local
complications (table 5).

**DISCUSSION**

This study demonstrates that the duration of organ failure is
a powerful marker of subsequent poor outcome in acute
pancreatitis. The patient group studied was large, and was
drawn from a wide range of hospitals. The findings therefore
are likely to be representative of patients with predicted
severe pancreatitis. The database used for this analysis has
been reported previously. 13 In that report, there was no
overall difference in mortality rate between the treatment
and placebo groups, so we feel it is unlikely that treatment
given in the trial will have affected the present observations.
We have included in the present report all patients initially
diagnosed as predicted severe acute pancreatitis including
those (three patients) who died and were found to have an
incorrect diagnosis. This ensures that our findings accurately
reflect the clinical situation.

We reiterate an important observation that selection of a
group of patients with predicted severe acute pancreatitis
using the APACHE-II score will identify many patients who
already have organ failure. In this database, patients were
selected with an APACHE-II score >6, according to the
protocol of the previously described trial. 11 Despite the lower
threshold used here than the cut off level (>8) suggested in
the Atlanta criteria, 744% of patients had organ failure at
entry to the study and over 50% had signs of organ failure
within the first 24 hours. The proven value of APACHE-II as a
predictor of severe acute pancreatitis 12 probably relates to the
ability of this system to identify early organ failure. Our data
show that even with the lower cut off, there is a high
subsequent rate of organ failure or local complications: 186 of
290 (64%) had severe pancreatitis, as defined at Atlanta.
Within this group of patients with predicted severe disease,
the persistence of organ failure during the first week of
hospital treatment is a powerful marker of fatal outcome.
Mortality rate in patients with persistent organ failure was
35% (table 2), much greater than the mortality rate of 18%
observed in patients with an initial APACHE-II score >8.


data*  

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Table 5 Relationship between duration of organ failure and development of local complications in 110 patients with record of a severe adverse event

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

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*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 6 that
the progress of the organ failure itself could be a useful
marker of disease severity. Butler and colleagues 6 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
did not come to the attention of study in hospital admission limits
the usefulness of systemic organ failure as a marker of response
to treatment in randomised trials, it has been suggested 6 that
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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.
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

MEMBERS OF THE BRITISH ACUTE PANCREATITIS STUDY GROUP

Professor D Alderson, Bristol Royal Infirmary; Mr A Berry, Northampton General Hospital; Dr D Breen, Royal Hallamshire Hospital, Sheffield; Mr J Britton, John Radcliffe Hospital, Oxford; Mr C Brown, Derriford Hospital, Plymouth; Professor FC Campbell, Ninewells Hospital, Dundee and The Medical School, Newcastle; Mr R Edmonson, Lewisham Hospital; Mr K Fearon, Edinburgh Royal Infirmary; Dr C Garrard, John Radcliffe Hospital, Oxford; Professor CW Imrie, Glasgow Royal Infirmary; Professor A Kingsnorth, Royal Liverpool Hospital and Derriford Hospital, Plymouth; Mr M Larvin, Leeds General Infirmary; Mr DM Lloyd, Leicester Royal Infirmary; Mr C McKay, Glasgow Royal Infirmary; Professor MJ McMahon, Leeds General Infirmary; Professor JP Neoptolemos, Queen Elizabeth Hospital, Birmingham; Professor BJ Rowlands, Royal Victoria Hospital, Belfast; Mr S Shimi, Ninewells Hospital, Dundee; Mr R Sutton, Royal Liverpool Hospital; Dr D Thomas, Morriston Hospital, Swansea; Mr RA L Young, West Middlesex University Hospital.

REFERENCES
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EDITOR’S QUIZ: GI SNAPSHOT

Robin Spiller, Editor

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 × 10⁹/L, platelets 337 × 10⁹/L, prothrombin time 14.8 seconds, and α fetoprotein 3.1 IU/L. A contrast enhanced computerised 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:
S Sebastian, D Tuite, P Crotty, W Torreggiani, M J Buckley
Adelaide and Meath Hospital, Dublin, Ireland

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