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ADVANCING THE FRONTIERS OF CLINICAL MANAGEMENT IN ACUTE PANCREATITIS

Maxim S Petrov

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy,
The University of Auckland, 2011
Acute pancreatitis has been known as a distinct clinical entity for more than a century, but the frontiers of its clinical management have not yet advanced enough to curb the high morbidity, mortality and cost of treatment in this disease. The management may principally be advanced either by detecting a specific therapeutic modality for acute pancreatitis or making better use of established non-specific modalities. This thesis aims to advance two frontiers of clinical management: classification of acute pancreatitis severity (which is an essential prerequisite for assessing the efficacy of a new therapeutic modality) and optimisation of enteral nutrition (the most promising non-specific modality in acute pancreatitis to date).

Past severity classifications were based on empirical description of events deemed to be associated with severity. There has been little progress in regards to a sound scientific foundation on which to base classification of acute pancreatitis severity. In this thesis, the concept of causal inference is applied to classifying the severity of acute pancreatitis, and the best available evidence suggests that classification of severity should be based on local and systemic determinants. Local determinants relate to whether there is (peri)pancreatic necrosis or not, and if present, whether it is sterile or infected. Systemic determinants relate to whether there is organ failure or not, and if present whether it is transient or persistent. Derivation of a classification based on available evidence for determinants of severity and the possibility of their interaction results in four categories of severity, i.e., “mild”, “moderate”, “severe”, and “critical”.

Maxim S Petrov
December 2011
Enteral nutrition is a rapidly evolving frontier in the management of acute pancreatitis. This thesis demonstrates that enteral nutrition given via the nasogastric route is safe and well tolerated in most patients with acute pancreatitis. Further, when given within 24 hours of admission to patients with mild to moderate acute pancreatitis, it results in significantly reduced intensity and duration of initial abdominal pain, need for opiates, and risk of oral refeeding intolerance. Lastly, use of a relatively inexpensive polymeric formulation is as safe and effective as a more costly elemental formulation.
The term “frontier” was originally used to epitomise the history of colonisation of the Great West in the United States in the late 17th to early 20th centuries. The continuous recession of arable lands and advance of settlements westward are seen by many historians as the driver of change which contributed significantly to the development of American society at that time. Later, the term was also adopted by John F Kennedy in his 1960 presidential campaign. In one of his speeches, he noted that "today some would say ... that all the horizons have been explored, that all the battles have been won, that there is no longer an American frontier. But ... the problems are not all solved and the battles are not all won, and we stand today on the edge of a new frontier - the frontier of the 1960s, a frontier of unknown opportunities and paths, a frontier of unfulfilled hopes and threats."

As in history, so too in pancreatology there remain significant frontiers that present opportunities for better outcomes in patients with acute pancreatitis. The most frequent disease of the pancreas, acute pancreatitis, has been recognised as a distinct clinical entity for more than 120 years. There has been extensive experimental and clinical research into this disease, seeking ways to improve the management and outcomes of patients with acute pancreatitis. However, as happens not infrequently in clinical science, the exponential growth of knowledge is followed by a levelling off, because certain concepts become unquestionable dogmas (the frontiers are declared closed), thereby limiting further qualitative growth of knowledge and rendering the care of patients suboptimal. The present work advances some of the contemporary frontiers in the clinical management of patients
with acute pancreatitis. It is invigorated by what William P Longmire, a doyen of hepatobiliary-pancreatic surgery in North America, once said “The pancreas, more than any other abdominal organ, continues to provide fascinating surgical frontiers...”
ACKNOWLEDGEMENTS

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LIST OF PEER-REVIEWED PUBLICATIONS (2008-2011)


• Petrov MS. Predicting the severity of acute pancreatitis: Choose the right horse before hitching the cart. *Dig Dis Sci.* 2011; 56:3402-3404.
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<table>
<thead>
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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>AP</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>APACHE</td>
<td>Acute physiology and chronic health evaluation</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>ETF</td>
<td>Early tube feeding</td>
</tr>
<tr>
<td>ERCP</td>
<td>Endoscopic retrograde cholangiopancreatography</td>
</tr>
<tr>
<td>FNA</td>
<td>Fine-needle aspiration</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
</tr>
<tr>
<td>IPN</td>
<td>Infected pancreatic necrosis</td>
</tr>
<tr>
<td>NBM</td>
<td>Nil-by-mouth</td>
</tr>
<tr>
<td>OF</td>
<td>Organ failure</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sepsis-related organ failure assessment</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>WCC</td>
<td>White cell count</td>
</tr>
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</table>
Chapter 1

CONTEMPORARY FRONTIERS IN ACUTE PANCREATITIS

1.1 Epidemiology of acute pancreatitis

Acute pancreatitis (AP) is a common digestive disease and the most frequent disorder of the pancreas. It is observed in every part of the world, but the incidence of AP varies considerably between countries. Relatively low figures are reported from the United Kingdom (9.8 cases per 100,000 population per year\(^1\)), Germany (13.1 cases per 100,000 population per year\(^2\)), and Japan (15.4 cases per 100,000 population per year\(^3\)). Medium figures are reported from New Zealand (29.3 cases per 100,000 population per year\(^4\)), Iceland (32.3 cases per 100,000 population per year\(^5\)), and Norway (34.4 cases per 100,000 population per year\(^6\)). The highest figures in the literature are reported from the United States (73.0 cases per 100,000 population per year\(^7\)) and Finland (73.4 cases per 100,000 population per year\(^8\)). However, direct comparison of incidences between countries is hardly legitimate because of diagnostic, aetiological, ethnic, and other differences between the study populations.

Several reports from the United States and Western Europe indicate that the frequency of this disease has increased dramatically. In the United States, there were significant upward trends in both absolute numbers of hospitalisations for AP and annual incidence. The absolute number of admissions was 101,000 in 1988 as compared with
201,000 in 2002. The annual incidence was also lowest in 1988 at 41 cases per 100,000 population and peaked in 2002 at 73 cases per 100,000 population. In Denmark, the annual incidence increased from 17 cases per 100,000 population in 1981 to 32 cases per 100,000 population in 2000. Similarly, in Sweden, the annual incidence increased from 18 cases per 100,000 population in 1985 to 35 cases per 100,000 population in 1999.

Most studies reporting on trends also indicate a steady decrease in the case-fatality rate over time. The case fatality for AP has decreased from 15%–21% in the earlier studies to 2%–7% in the recent studies. Although the case-fatality rate has decreased, several studies have reported that the population mortality rate has remained unchanged over time. The likely explanation for this is that, given that the case-fatality rate is a proportion of deaths within a designated population of people with AP and the population mortality is a rate per 100,000 population, better detection of mild cases within a population results in a decrease in case-fatality but not in the population mortality rate. In addition, a proportional increase in the number of non-mild AP cases from an increase in the incidence may be offset by a decrease in mortality from earlier recognition and better treatment of local and systemic complications over time.

Patients with AP also pose a considerable financial burden to health care systems. An earlier study of patients with necrotising pancreatitis from the United Kingdom estimated that the actual cost of treatment ranged from £9296 to £33,796, of which two thirds was attributable to hospitalisation, 20% to surgical and endoscopic interventions, and 16% to investigations. A recent study from the United States estimated that the total cost of AP admissions in 2003 was $2.2 billion (95%
confidence interval [CI] 2.0–2.3 billion).\textsuperscript{14} Further, mean cost per hospitalisation was $9870 (95% CI 9300–10,400) and mean cost per hospital day was $1670 (95% CI 1620–1720).

Altogether, these epidemiological figures indicate that AP is a common, potentially fatal, and costly disease. There is no room for complacency, and the frontiers in clinical management need to be expanded if the burden of this disease is to be reduced in a meaningful way.

1.2 Classifying the severity of acute pancreatitis

Most patients with mild AP have an uneventful, self-limited course of disease and are discharged from hospital within a few days. In contrast, patients with other than mild AP have local and/or systemic complications and are at risk of death. One of the ways to improve outcomes in the latter category of patients is to quest and recognise a specific treatment for AP. The important prerequisite for recognising the efficacy of a specific treatment is an accurate classification of actual severity, because this is essential for enrolment of patients in clinical trials, assessment of the effect of treatment, and comparison between patient populations in different institutions.\textsuperscript{15} To do otherwise, and in particular to use an inaccurate classification of severity, may lead to failures in recognising a beneficial effect of effective treatments because the selected study populations might be suboptimal (e.g., too broad) and/or the endpoints used for assessment of the treatment’s effect might be suboptimal (e.g., not prevalent) and/or the comparison (aggregation) of inter-institutional data might be invalid (e.g.,
clinical heterogeneity in meta-analyses). As George Bernard Shaw aptly stated, “Crude classifications and false generalizations are the curse of organized life”.

The first published classification of AP severity dates back to 1983 when an international meeting on classification of pancreatitis was held in Cambridge. It was recognised that acute and chronic pancreatitis are essentially distinct entities. Further, the Cambridge classification addressed the issue of severity by distinguishing “mild” and “severe” AP. The latter was defined as “multisystem failure and/or early or late local complications” and “mild” AP was defined as “no multisystem failure with uncomplicated recovery”. The recognised local complications were pancreatic phlegmon, pseudocyst, and abscess.

One year later, a meeting in Marseilles gave special emphasis to the morphological features of AP. “Severe” AP was defined as “extensive peri and intra-pancreatic necrosis, parenchymal necrosis and haemorrhage, localised or diffuse” and “mild” AP as “peripancreatic fat necrosis and interstitial edema, absence of pancreatic necrosis”. Possible impairment of exocrine and endocrine function was also mentioned in the classification. It also stated that in “severe” AP, “scarring and pseudocysts may persist”.

More details were added to the Marseilles classification at the meeting in Rome in 1988. They mainly related to pancreatic and peripancreatic collections in AP. As a result, the definition of “mild” AP remained unchanged, while “severe” AP was defined as “extensive peri and intra-pancreatic necrosis, parenchymal necrosis and
hemorrhage, localised or diffuse, peripancreatic fluid collections, infection of necrosis, formation of pseudocysts or abscesses”.

In 1992, the Atlanta symposium focused exclusively on AP and attempted to devise a classification of severity that would be suitable for both routine clinical practice and comparison of inter-institutional data. The Atlanta classification adopted the same two categories for classifying AP severity and added some special definitions regarding acute fluid collection, pancreatic necrosis, pancreatic pseudocyst, and pancreatic abscess. It also recommended the use of predictive tools, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Ranson criteria. As a result, “severe” AP was defined as being “associated with organ failure (OF) and/or local complications, such as necrosis, abscess, or pseudocyst and characterised by three or more Ranson criteria, or eight or more APACHE II criteria” and “mild” AP as “associated with minimal organ dysfunction and an uneventful recovery, and it lacks the features of severe AP”.

The latest available revision of the Atlanta definitions stated that “severe” AP is defined as “death or persistent OF or prolonged hospitalisation requiring supportive treatment and/or active intervention” and “mild” AP as “no death, no persistent OF, and no prolongation of hospitalisation (> 1 week)”.

Table 1.1 summarises the entities that were included in the definitions of “severe” AP in previous classifications of AP severity.
### Table 1.1 Entities included in the definition of “severe” acute pancreatitis in previous classifications

<table>
<thead>
<tr>
<th>Classification</th>
<th>Year</th>
<th>Local entities</th>
<th>Systemic entities</th>
<th>Other entities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambridge(^{16})</td>
<td>1983</td>
<td>Pancreatic phlegmon</td>
<td>and/or Multisystem failure</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic pseudocyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic abscess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marseilles(^{17})</td>
<td>1984</td>
<td>Peripancreatic necrosis</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parenchymal necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic haemorrhage</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pancreatic scarring</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic pseudocyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marseilles-Rome(^{18})</td>
<td>1988</td>
<td>Peripancreatic necrosis</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parenchymal necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripancreatic fluid collections</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection of necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic abscess</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic pseudocyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atlanta(^{19})</td>
<td>1992</td>
<td>Pancreatic necrosis</td>
<td>and/or Respiratory failure</td>
<td>APACHE II ≥ 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic abscess</td>
<td>Renal failure</td>
<td>Ranson ≥ 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic pseudocyst</td>
<td>Shock</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastrointestinal bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypocalcaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coagulopathy</td>
<td></td>
</tr>
<tr>
<td>Revised Atlanta(^{22})</td>
<td>2009</td>
<td>-</td>
<td>Persistent organ failure</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and/or Prolonged hospitalisation</td>
<td></td>
</tr>
</tbody>
</table>
1.3 Early management of acute pancreatitis

While a specific treatment for AP is still awaited, the other way to improve outcomes in patients with non-mild AP is to make better use of existing non-specific modalities. Given that the disease is often still in evolution at the time of hospital admission, early treatments and/or preventive strategies appear to be crucial because they offer an opportunity to alter the natural course of the disease.\textsuperscript{23,24} This is commonly referred to as a “therapeutic window”, and the following paragraphs will delineate the best available evidence (randomised controlled trials [RCT] and meta-analyses of RCTs) on the use of current preventive and treating modalities in AP, i.e., the potential frontiers in clinical management that could be expanded.

1.3.1 Analgesia

Pain is the cardinal symptom of AP and its relief is a clinical priority. Different analgesics have been compared in patients with AP, and the six published RCTs are summarised in Table 1.\textsuperscript{25-30} These trials had different study designs, evaluated different analgesics, had small sample sizes, and only half of the trials were double-blinded. From these studies, it can be said that there is no credible clinical evidence to avoid the use of morphine in treating the pain associated with AP. The evidence would suggest that the nonsteroidal anti-inflammatory drug of choice is metamizole (2 g/8 hours intravenously) and the opioid of choice is buprenorphine (0.3 g/4 hours intravenously).
### Table 1.2 Randomised controlled trials of analgesics in patients with acute pancreatitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Setting</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Patients(n)</th>
<th>Allocation concealment</th>
<th>Reduction of pain score</th>
<th>Other important findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blamey et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>1984</td>
<td>UK</td>
<td>Buprenorphine (i.m.)</td>
<td>Pethidine (i.m.)</td>
<td>17</td>
<td>15</td>
<td>Single-blind</td>
<td>No difference</td>
</tr>
<tr>
<td>Ebbehoj et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>1985</td>
<td>Denmark</td>
<td>Indomethacin (rectal)</td>
<td>Placebo (rectal)</td>
<td>14</td>
<td>16</td>
<td>Double-blind</td>
<td>Significantly greater in the intervention group over the first 16 hours</td>
</tr>
<tr>
<td>Jakobs et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2000</td>
<td>Germany</td>
<td>Buprenorphine (i.v.)</td>
<td>Procaine (i.v.)</td>
<td>20</td>
<td>20</td>
<td>Open-label</td>
<td>Significantly greater in the intervention group over the first 48 hours</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Intervention 1</td>
<td>Control</td>
<td>N1</td>
<td>N2</td>
<td>Study Design</td>
<td>Findings</td>
</tr>
<tr>
<td>------------------</td>
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<td>------------------</td>
<td>-----</td>
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<td>--------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Stevens et al</td>
<td>2002</td>
<td>USA</td>
<td>Fentanyl (transdermal)</td>
<td>Placebo (transdermal)</td>
<td>16</td>
<td>16</td>
<td>Double-blind</td>
<td>Significantly greater in the intervention group between 36 and 60 hours</td>
</tr>
<tr>
<td>Kahl et al</td>
<td>2004</td>
<td>Germany</td>
<td>Pentazocine (i.v.)</td>
<td>Procaine (i.v.)</td>
<td>50</td>
<td>51</td>
<td>Open-label</td>
<td>Significantly greater in the intervention group over the first 72 hours</td>
</tr>
<tr>
<td>Peiro et al</td>
<td>2008</td>
<td>Spain</td>
<td>Metamizole (i.v.)</td>
<td>Morphine (s.c.)</td>
<td>8</td>
<td>8</td>
<td>Open-label</td>
<td>Non-significantly greater in the intervention group over the first 24 hours</td>
</tr>
</tbody>
</table>

**Abbreviations:** i.m., intramuscularly; i.v., intravenously; LOS, length of stay; s.c., subcutaneously
Although it has been reported that analgesics can also be given transdermally or rectally, there are no RCTs comparing the different routes of administration of the same analgesic in patients with AP. Despite evidence from RCTs being available, there remains uncertainty about the preferred analgesic and the best method of administration. Consequently, there are no recent guidelines relating to the management of AP that provide a specific recommendation regarding optimal pain management.31

1.3.2 Fluid resuscitation

Fluid resuscitation is thought to be one of the most important aspects of the early management of AP and is the intervention most likely to improve outcome.32,33 Unfortunately, only three RCTs have been conducted in this area so far, two of which have been executed in China34,35 and one in the United States36. The first study from China compared two rates of fluid infusion, i.e., 10–15 mL·kg⁻¹·h⁻¹ versus 5–10 mL·kg⁻¹·h⁻¹, and found that the latter resulted in a significantly lower rate of infectious complications and mortality.35 The second study from China compared the effect of “rapid” (haematocrit < 35%) versus “slow” (haematocrit ≥ 35%) haemodilution within 48 hours of onset. The study showed that a target haematocrit of more than 35% is associated with a significantly lower rate of infectious complications and mortality.34 The Chinese RCTs were followed by a small RCT from the United States in which four regimens were compared, i.e., goal-directed fluid resuscitation with lactated Ringer's solution, goal-directed fluid resuscitation with normal saline, standard fluid resuscitation with lactated Ringer's solution, and standard fluid resuscitation with normal saline.36 It was shown that, while goal-directed resuscitation did not
significantly reduce the incidence of systemic inflammatory response syndrome (SIRS) in comparison with standard resuscitation, there was a significant reduction in SIRS after 24 hours among patients who received lactated Ringer's solution rather than normal saline.

Apart from these three RCTs, there is no other evidence regarding the optimal resuscitation fluid, the required fluid rate, or the best marker to guide fluid therapy and indicate the adequacy of resuscitation. It is also not known whether colloids or crystalloids are more effective in improving pancreatic microcirculation and outcomes.

1.3.3 Antibiotics

While the use of broad-spectrum antibiotics to treat established infection in AP is a well established practice, the use of prophylactic antibiotics has been controversial for decades. Three RCTs in the 1970s failed to demonstrate a beneficial effect of antibiotic prophylaxis, probably due to a small sample size, inappropriate selection of antibiotics (e.g., ampicillin, which does not sufficiently penetrate the pancreas) and inclusion of patients with mild pancreatitis (Table 1.3). 37–39 Between 1993 and 2009, several randomised, controlled, open-label trials were published evaluating the efficacy of prophylactic antibiotic treatment in patients with predicted severe AP. 40–46 The results of these RCT trials were conflicting, in that some demonstrated a significant reduction of infectious complications and mortality with the use of prophylactic antibiotics, while others failed to do so (Table 1.3).
### Table 1.3 Randomised controlled trials of intravenous antibiotic prophylaxis versus no antibiotics in patients with acute pancreatitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Setting</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Patients (n)</th>
<th>Allocation concealment</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howes et al37</td>
<td>1975</td>
<td>USA</td>
<td>Ampicillin</td>
<td>None</td>
<td>48</td>
<td>47</td>
<td>Open-label No significant difference in any outcome</td>
</tr>
<tr>
<td>Craig et al38</td>
<td>1975</td>
<td>USA</td>
<td>Ampicillin</td>
<td>None</td>
<td>23</td>
<td>23</td>
<td>Open-label No significant difference in any outcome</td>
</tr>
<tr>
<td>Finch et al39</td>
<td>1976</td>
<td>USA</td>
<td>Ampicillin</td>
<td>Placebo</td>
<td>31</td>
<td>27</td>
<td>Double-blind No significant difference in any outcome</td>
</tr>
<tr>
<td>Pederzoli et al40</td>
<td>1993</td>
<td>Italy</td>
<td>Imipenem</td>
<td>None</td>
<td>41</td>
<td>33</td>
<td>Open-label Significantly lower rate of pancreatic infection in the intervention group</td>
</tr>
<tr>
<td>Sainio et al41</td>
<td>1995</td>
<td>Finland</td>
<td>Cefuroxime</td>
<td>None</td>
<td>30</td>
<td>30</td>
<td>Open-label Significantly lower mortality rate, but not pancreatic infection, in the intervention group</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Combination</td>
<td>Comparator</td>
<td>N Intervention</td>
<td>N Control</td>
<td>Study Design</td>
</tr>
<tr>
<td>-------------------------------------------</td>
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</tr>
<tr>
<td>Delcenserie et al(^{42})</td>
<td>1996</td>
<td>France</td>
<td>Ceftazidime + amikacin + metronidazole</td>
<td>None</td>
<td>11</td>
<td>12</td>
<td>Open-label</td>
</tr>
<tr>
<td>Schwarz et al(^{43})</td>
<td>1997</td>
<td>Germany</td>
<td>Ofloxacin + metronidazole</td>
<td>None</td>
<td>13</td>
<td>13</td>
<td>Open-label</td>
</tr>
<tr>
<td>Spicak et al(^{46})</td>
<td>2003</td>
<td>Czech Republic</td>
<td>Meropenem</td>
<td>None</td>
<td>20</td>
<td>21</td>
<td>Open-label</td>
</tr>
<tr>
<td>Isenmann et al(^{47})</td>
<td>2004</td>
<td>Germany</td>
<td>Ciprofloxacin + metronidazole</td>
<td>Placebo</td>
<td>58</td>
<td>56</td>
<td>Double-blind</td>
</tr>
<tr>
<td>Dellinger et al(^{48})</td>
<td>2007</td>
<td>North America and Europe</td>
<td>Meropenem</td>
<td>Placebo</td>
<td>50</td>
<td>50</td>
<td>Double-blind</td>
</tr>
<tr>
<td>Rokke et al(^{44})</td>
<td>2007</td>
<td>Norway</td>
<td>Imipenem</td>
<td>None</td>
<td>36</td>
<td>37</td>
<td>Open-label</td>
</tr>
<tr>
<td>Xue et al(^{45})</td>
<td>2009</td>
<td>China</td>
<td>Imipenem</td>
<td>None</td>
<td>29</td>
<td>27</td>
<td>Open-label</td>
</tr>
<tr>
<td>Garcia-Barrasa et al(^{49})</td>
<td>2009</td>
<td>Spain</td>
<td>Ciprofloxacin</td>
<td>Placebo</td>
<td>22</td>
<td>19</td>
<td>Double-blind</td>
</tr>
</tbody>
</table>
Only three double-blind, placebo-controlled, randomised trials were published and all of them were unable to show a beneficial effect of antibiotic prophylaxis in regard to infectious pancreatic complications, need for surgery, and mortality.\textsuperscript{47–49} This is in line with the findings of a meta-analysis that showed an inverse relationship between methodological quality of the studies and impact of antibiotic prophylaxis on mortality.\textsuperscript{50} On the other hand, it is worth noting that the three double-blind RCTs mentioned were not without flaws. These include a large crossover to open-label antibiotics in the control group (i.e., a high percentage of patients in the placebo group who were treated with intravenous antibiotics) and inclusion of patients on the basis of predicted severity of AP rather than proven necrotising pancreatitis. All of the studies were underpowered, since the power calculation was based on an infection rate of 40%, whereas the actual infection rates in the placebo groups of the trials were only 12\%–17\%.\textsuperscript{51,52}

There have been many statistical attempts to aggregate the data on use of prophylactic antibiotics in AP. Moreover, it appears that the number of meta-analyses to address this question has outgrown the number of RCTs. In particular, while only two new RCTs were published in 2006–2007, it is notable that seven of the 10 meta-analyses were published within this period.\textsuperscript{53} There were 13 RCTs included in these seven meta-analyses.\textsuperscript{50,54–59} Because of the different inclusion criteria and various meta-analytic techniques used, there is a lack of concordance, and the studies provide contradictory recommendations regarding the role of prophylactic antibiotics in reducing the risk of infectious pancreatic complications. Overall, it appears that the most recent studies do not support the use of prophylactic antibiotics to reduce the
frequency of infectious pancreatic complications, surgical intervention, and mortality in patients with AP.

1.3.4 Therapeutic ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy has been promoted as an effective intervention in patients with acute biliary pancreatitis since the early 1990s. This was based on the findings of two RCTs, one from the United Kingdom and the other from Hong Kong, of early (within 24–48 hours of admission) ERCP ± sphincterotomy versus conservative treatment.\textsuperscript{60,61} Both trials demonstrated that early ERCP was associated with a reduction in complications but not mortality, and the benefits were only observed in patients with predicted severe AP.

There is some evidence to suggest that the duration of biliary obstruction, rather than the predicted severity of AP, is the most important factor that influences outcome in patients with biliary pancreatitis.\textsuperscript{62,63} This is probably due to the increased likelihood of concomitant cholangitis with prolonged obstruction, and might be the best explanation for the usefulness of ERCP in the management of acute biliary pancreatitis. The first and only multicentre RCT to examine the role of ERCP in AP was designed to include only patients without evidence of obvious biliary obstruction, defined as a serum bilirubin level higher than 5 mg/dL (90 µmol/L).\textsuperscript{64} This German study did not find any benefit for early ERCP (within 72 hours after onset of symptoms) over conservative treatment. The most recent RCT, from Argentina, found that early ERCP in patients with biliary obstruction, defined by laboratory and
radiological criteria, and without evidence of acute cholangitis, conferred no benefit either.\textsuperscript{65}

Two important meta-analyses were published in 2008.\textsuperscript{66,67} The first found that early ERCP, when compared with conservative treatment, did not decrease the incidence of local pancreatic complications or the mortality rate in patients with biliary AP.\textsuperscript{67} The second meta-analysis was designed to negate the confounding effect of acute cholangitis and demonstrated no benefit of early ERCP over conservative treatment in terms of complications and mortality in patients with biliary AP.\textsuperscript{66} The conclusion to be drawn from these studies is that early ERCP is indicated in patients with AP if there is clinical evidence of acute cholangitis but not for those with cholestasis alone. While cholestasis can reflect a persisting main bile duct stone, it might also be due to oedema of the ampulla secondary to recent stone passage to the duodenum, and thus be expected to improve over the first few days of admission.\textsuperscript{62} Persistent cholestasis without cholangitis may require ERCP, but not usually in the acute setting.

1.3.5 Nutrition

The importance of providing nutritional support in patients with AP has been known since the 1970s. Parenteral nutrition was regarded as the standard of nutritional management for nearly four decades due to the advocacy of the “pancreas rest” concept. The rationale for this concept was to rest the inflamed pancreas, thereby preventing stimulation of exocrine function and release of proteolytic enzymes.\textsuperscript{68,69} However, critics argued that, in addition to cost and catheter-related sepsis, parenteral nutrition might lead to electrolyte and metabolic disturbances, gut barrier alteration,
and increased intestinal permeability. \textsuperscript{24,70,71} Comparison of total parenteral nutrition and total enteral nutrition in patients with predicted severe AP was the subject of eight RCTs (Table 1.4). \textsuperscript{72–79} The results were statistically aggregated in several meta-analyses, all of which demonstrated the benefits of enteral over parenteral nutrition. \textsuperscript{80–83} In particular, a meta-analysis of high-quality RCTs only has shown a significant 2.0-fold reduction in the risk of total and pancreatic infectious complications and a 2.5-fold reduction in the risk of death in patients receiving total enteral nutrition. \textsuperscript{83}
Table 1.4 Randomised controlled trials of total enteral versus total parenteral nutrition in patients with predicted severe acute pancreatitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Setting</th>
<th>Patients (n)</th>
<th>Allocation concealment</th>
<th>Reduction of infectious complications and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalfarentzos et al\textsuperscript{74}</td>
<td>1997</td>
<td>Greece</td>
<td>18 20</td>
<td>Open-label</td>
<td>Significantly lower rate of pancreatic infection in the total enteral nutrition group</td>
</tr>
<tr>
<td>Gupta et al\textsuperscript{73}</td>
<td>2003</td>
<td>UK</td>
<td>8 9</td>
<td>Open-label</td>
<td>Non-significantly lower rate of pancreatic infection in the total enteral nutrition group</td>
</tr>
<tr>
<td>Louie et al\textsuperscript{72}</td>
<td>2005</td>
<td>Canada</td>
<td>10 18</td>
<td>Open-label</td>
<td>Non-significantly lower rate of pancreatic infection in the total enteral nutrition group</td>
</tr>
<tr>
<td>Eckerwall et al\textsuperscript{75}</td>
<td>2006</td>
<td>Sweden</td>
<td>23 25</td>
<td>Open-label</td>
<td>No significant difference in outcomes</td>
</tr>
<tr>
<td>Petrov et al\textsuperscript{76}</td>
<td>2006</td>
<td>Russia</td>
<td>35 34</td>
<td>Open-label</td>
<td>Significantly lower rate of pancreatic infection and mortality in the total enteral nutrition group</td>
</tr>
<tr>
<td>Casas et al\textsuperscript{77}</td>
<td>2007</td>
<td>Spain</td>
<td>11 11</td>
<td>Open-label</td>
<td>Non-significantly lower rate of pancreatic infection in the total enteral nutrition group</td>
</tr>
<tr>
<td>Doley et al\textsuperscript{78}</td>
<td>2008</td>
<td>India</td>
<td>25 25</td>
<td>Open-label</td>
<td>No significant difference in the outcomes</td>
</tr>
<tr>
<td>Wu et al\textsuperscript{79}</td>
<td>2010</td>
<td>China</td>
<td>53 54</td>
<td>Open-label</td>
<td>Significantly lower rate of pancreatic infection and mortality in the total enteral nutrition group</td>
</tr>
</tbody>
</table>
Despite the evident clinical benefits of enteral over parenteral nutrition in terms of the reduction in risk of infectious complications and mortality, the exact mechanism of its favourable effect remains unclear. It is believed that enteral nutrition may prevent or attenuate the mucosal barrier breakdown and subsequent bacterial translocation that play a pivotal role in the development of infectious complications in the course of severe AP.\textsuperscript{71,84} When monitoring mucosal barrier function, permeability of the structural mucosal barrier is often the main parameter measured. Unfortunately, there is no consistency in the clinical studies with regard to gut permeability. On the one hand, three clinical studies of AP showed increased intestinal permeability to both micromolecules and macromolecules in patients with predicted severe AP when compared with predicted mild AP and healthy volunteers.\textsuperscript{85–87} On the other hand, the RCT by Powell and colleagues, in which patients with predicted severe AP were randomised to receive either enteral nutrition or no artificial nutritional support, showed significantly increased intestinal permeability by day 4 in patients allocated to the enteral nutrition group.\textsuperscript{88} Similarly, the RCT of nasogastric versus parenteral feeding in predicted severe patients by Eckerwall and colleagues demonstrated impaired gut permeability on day 3 in the enteral nutrition group.\textsuperscript{75} However, in fact, both RCTs included a considerable number of patients with mild AP (11 of 27 and 26 of 48, respectively), in which it is unlikely that intestinal permeability changed considerably.

Furthermore, concentrations of anti-endotoxin core antibodies for immunoglobulin M (IgM) were also used as an indirect marker for intestinal permeability. Results of the RCT by Windsor and colleagues showed that serum IgM antibodies decreased significantly following 7 days of enteral nutrition when compared with the parenteral
nutrition group (p < 0.05). Similarly, the RCT by Gupta and colleagues demonstrated that IgM antibodies fell significantly in the enteral nutrition group (p = 0.03) and tended to rise in the parenteral nutrition group over the week of treatment. Conversely, the RCT by Eckerwall and colleagues found decreasing levels of IgM antibodies in both the enteral nutrition and parenteral nutrition groups, with no significant difference at any time point during ten days of observation. The mechanism of beneficial influence of enteral nutrition in AP warrants further investigation, and more studies on the use of enteral nutrition in patients with AP are needed.

1.4 Summary

AP is a common disease with an increasing incidence. Still high morbidity and mortality in this disease as well as the overwhelming cost of treatment indicate significant room for improvement in clinical management. There are two principal ways to advance clinical management. The first relates to discovering a new specific therapeutic modality for AP and the second relates to making better use of established non-specific modalities.

The essential prerequisite for assessing the efficacy of a new therapeutic modality is the use of an accurate state-of-the-art classification of severity. Classification has evolved over time and incorporated important developments in the field, such as recognition that acute and chronic pancreatitis are distinct entities, introduction and widespread use of computed tomography (CT), and a better understanding of the role of systemic factors in AP. However, despite continuously expanding knowledge on the
complexity of this disease, classification remains empirical, static ("end-of-episode"), and binary. The development of a new classification of AP severity based on sound clinical and epidemiological grounds will be presented in this thesis.

While there is no specific therapy for patients with AP as yet, adequate early treatment with established non-specific modalities has led to improved outcomes. There have been several recent advances in the early non-specific management of AP. These include emergence of RCTs on fluid resuscitation and analgesia, more data (albeit conflicting) on the prophylactic use of antibiotics, and restriction of indications for early therapeutic ERCP to patients with co-existing acute cholangitis. However, the most notable and consistent improvement in outcomes over the last decade has come from the use of enteral tube feeding in patients with AP. Moreover, considerable opportunities for improvement remain in this area, and thus optimisation of enteral nutrition in AP will be the focus of the following chapters of this thesis.
Chapter 2

NEW FRONTIERS IN CLASSIFYING SEVERITY AND USE OF ENTERAL NUTRITION IN ACUTE PANCREATITIS

2.1 Statement of the problem

There are many questions that remain unresolved in the management of patients with AP and, correspondingly, the frontiers of clinical management can potentially be expanded in several areas. This thesis will focus on two important areas of clinical management. The first is development of a clinically meaningful and epidemiologically sound classification of AP severity, which will underpin the ability of future research to discover a specific treatment for AP and make routine clinical management of patients with AP more tailored and evidence-based. The second is investigation of several topical questions pertinent to the use of enteral nutrition as part of the drive to provide more evidence-based clinical management of patients with AP.

2.1.1 Need for a new classification of severity

The literature review in Chapter 1 has shown that a total of five international classifications of AP severity have been proposed so far (Table 1.1). It is timely to look critically at the way the severity of AP is classified now, if we are to make
progress with the quest for a specific treatment in the future. The following paragraphs consider some of the limitations of the Atlanta classification, the most widely used classification of AP to date, and its revised definitions.19,22

The Atlanta classification was published in 1993, and the latest version of the revised Atlanta definition became publicly available in 2009.19,22 The major impetus to revision of the original Atlanta definition has been the recent significant advances in understanding the pathophysiology of AP, and, in particular, the role of systemic complications. While the original Atlanta definitions of “severe” AP included only the presence or absence of OF, it is increasingly recognised that the number of organs that fail, timing of onset, and duration of OF all relate to mortality. In particular, it has been shown that OF persisting beyond 48 hours is associated with significantly increased mortality in patients with AP.90,91 Therefore, the revised Atlanta definitions suggest that only patients with persistent OF should be defined as having “severe” AP.22 However, this means that patients with transient OF are considered to have “mild” AP and that local pancreatic complications are not considered to contribute to severity in patients with AP.

Since the first attempt to describe the severity of AP by Fitz in 1889 and until the most recent Atlanta symposium in 1992, a morphological component has always been included.19,92 While Fitz believed that the morphological features of severe disease were evidence of pancreatic haemorrhage and disseminated fat necrosis, the morphological features of severe disease in the Atlanta classification were pancreatic necrosis, abscess and pseudocyst. Since then, a number of studies have demonstrated that infection of pancreatic necrosis rather than presence of necrosis per se is
associated with high morbidity and mortality in patients with AP. Further, whereas in the past necrotising pancreatitis was described solely based on the presence of pancreatic parenchymal necrosis, a number of recent studies have demonstrated that there is a distinct subgroup of patients who develop peripancreatic necrosis without recognisable pancreatic parenchymal necrosis. These patients have significantly worse outcomes than patients with “mild” AP. Taking these arguments into account, it seems reasonable to redress the shortcoming of the revised Atlanta definitions and consider local pancreatic complications in classifying the severity of AP.

Another important shortcoming of the revised Atlanta definitions is that they are strongly predicated on the notion of a biphasic natural course of AP, and thus recommend that clinicians use a different method of classification for the early phase and the late phase of AP. In the early phase of the disease, the classification of severity is to be based on the presence or absence of persistent OF and/or death. In the late phase, the classification of severity is to be based on the need for “active intervention (operative, endoscopic, laparoscopic, or percutaneous) or other supportive measures (such as need for respiratory ventilation, renal dialysis, or nasojejunal feeding)” as well as the presence or absence of persistent OF and/or death. This approach appears to be suboptimal for the following reasons:

1. The two phase view is probably too simplistic for such an intricate, evolving, and dynamic disease as AP. Further, there is imprecision in the definition of the duration of the early phase as “within the first 1–2 weeks of onset”, which probably reflects the lack of consensus in the literature. Besides, a recent study of all deaths due
to AP in Scotland over a 6-year period did not reveal a bimodal distribution of mortality.\textsuperscript{108}

2. It is not applicable to all patients with AP. Particularly, patients who only develop OF in the late phase and those who only develop pancreatic complications in the early phase are not taken into account and thus are likely to be misclassified. The proportion of these patients is not negligible. A recent study from India of 59 patients with persistent OF found that 27 (46\%) developed it after 7 days of onset of AP,\textsuperscript{109} and an earlier study from Germany found infected pancreatic necrosis was present in 27 of 114 (24\%) patients during the first week of disease\textsuperscript{110}.

3. It cannot be applied on a daily basis, only at the end of the episode or at an arbitrary time point (7 days after onset of AP). Thus, classification lacks utility as a clinical tool to monitor the clinical trajectory of the individual patient during the course of AP and in response to treatment. It is worth noting that an objectively defined clinical trajectory may potentially be very important in deciding on the timing and nature of intervention (e.g., staged treatment of infected pancreatic necrosis).\textsuperscript{111}

4. Significant variance is inevitable using a classification of severity that is based on the need for an intervention or supportive care. This is because there is a lack of international standardisation of management, including the indications for endoscopic procedures, enteral nutrition, and criteria for admission to an intensive care unit (ICU).\textsuperscript{31}
5. The prognostic and clinical utility of many of the suggested new radiological terms (e.g., “acute peripancreatic fluid collection”, “acute post-necrotic collection”, “walled-off necrosis”) has not been demonstrated, and these may require further revision.\textsuperscript{103,112} Furthermore, there is no consensus on the use of this terminology even among radiologists, and an alternative image-based classification based on retroperitoneal extension has been proposed\textsuperscript{113,114}. Therefore, a suggestion that radiologists should refine their imaging criteria for the diagnosis of pancreatic complications and that clinicians should integrate them into a clinical classification system appears to be reasonable and justified\textsuperscript{115}.

Finally, it is striking that while all the classifications in the past invariably employed a binary approach to classification, more than 20 different entities have been used to describe “severe” AP (Table 1.1). The multiplicity of entities used to characterise only one category of severity in itself indicates lack of certainty and that there is considerable room for improvement. Further, it appears that the use of these entities for classifying the severity of AP has been merely based on empirical description, rather than an evidence-based approach. After more than a century of deliberation, there has not been sufficient progress in regards to a sound foundation on which to base the classification of AP severity, nor any attempt to determine whether there may be an advantage in defining more than two categories of severity.

2.1.2 Need for optimisation of enteral nutrition

The literature review in Chapter 1 has shown that there are several management variables that still require clinical investigation and optimisation. One of these is
enteral nutrition and its optimal delivery in patients with AP. To date, enteral nutrition is the only early management strategy that has been consistently demonstrated to be associated with significant reduction of mortality and morbidity in patients with AP.\textsuperscript{116,117} However, the RCTs of enteral nutrition in AP conducted in the past used a wide array of prediction criteria with different thresholds (Ranson score $\geq 3$, APACHE II score $\geq 8$, APACHE II score $\geq 7$, APACHE II score $\geq 6$, C-reactive protein (CRP) $> 150$ mg/L, CRP $> 120$ mg/L) to enrol patients.

Unfortunately, the field is hampered by suboptimal definitions of that for which prediction is sought. A recent systematic review showed that there was remarkable heterogeneity between the studies in this regard.\textsuperscript{118} The endpoints for the prediction of severity included multiple factor prognostic scores (APACHE II $\geq 8$ and/or Ranson $\geq 3$), death, local and/or systemic complications (as defined by the Atlanta symposium), Japanese criteria of severity, OF, pancreatic necrosis, infected pancreatic necrosis (IPN), length of hospitalisation, ICU admission, and need for surgery. This is one of the main reasons why modern prognostic scores can, on average, correctly predict severity in only 60\%-80\% of patients.\textsuperscript{119,120} Moreover, a recent RCT from a well known group with an interest in AP employed an APACHE II score $\geq 8$ to enrol patients with a predicted severe course of AP and found that actual severe AP (as defined by the Atlanta symposium) occurred in only 46\%.\textsuperscript{75} That is inferior to tossing a coin (and definitely more labour-intensive and time-consuming!) The important implication for nutritional management of patients with AP is that the exact (actual) population of patients with AP who benefit from enteral nutrition is still largely unknown.
Several other unanswered questions on nutrition in AP relate to the “pancreas rest” concept. The central tenet of this concept is that enteral nutrition delivered into any part of the upper gastrointestinal tract other than the jejunum stimulates pancreatic secretion and, consequently, exacerbates the severity of AP.\textsuperscript{68,121} It also postulates that any enteral nutrition formulation other than an elemental formulation causes stimulation of pancreatic secretion. Given that this concept remained unchallenged for decades, the majority of clinical studies in the field of AP were conducted using nasojejunal tube feeding and an elemental formulation. However, accumulating evidence from other fields, particularly critical care medicine, suggests that nasogastric feeding may be as safe and effective as nasojejunal feeding, at least in some patients.\textsuperscript{122–125} Similarly, there is a growing body of evidence that a polymeric formulation, immunonutrition, a fibre-enriched formulation, and probiotics may be a better alternative to an elemental formulation in diseases other than AP.\textsuperscript{126–129} Thus there is a need and justification for exploring questions concerning the optimal route of enteral nutrition delivery and the optimal enteral nutrition formulation to be used in patients with AP.

2.2 Thesis outline

The main body of this thesis can be broadly grouped into two parts. The first part (Chapters 3–6) describes the step-by-step derivation of the determinant-based classification of AP severity. The second part (Chapters 7–10) addresses key questions concerning the nutritional management of patients with AP.
A number of classifications of severity have been proposed and used over the last decades. However, none of them has been built upon a sound epidemiological background. Chapter 3 addresses this gap and applies the concept of causal inference into a context of classifying the severity of AP. This leads to the realisation that there is a novel category of severity, termed “critical” AP, which is validated in Chapter 4. The next chapter (Chapter 5) presents the results of a worldwide survey of pancreatologists which sought to define the perceived usefulness of the new category in particular and the concept as a whole. It also presents a global opinion on several important but, to date, poorly addressed questions pertinent to classifying the severity of AP. The concluding chapter of the first part (Chapter 6) presents the new determinant-based classification of severity as well as a set of definitions to operationalise it.

The second part opens with a chapter (Chapter 7) that explores the safety and efficacy of nasogastric tube feeding in patients with AP. The following two chapters present the rationale and methodology (Chapter 8) as well as the results and implications (Chapter 9) of the RCT that utilised the new classification of severity and investigated the safety and efficacy of early nasogastric tube feeding in comparison with a nil-by-mouth (NBM) regimen in patients with mild to moderate AP. The concluding chapter of the second part (Chapter 10) investigates the optimal enteral nutrition formulation in patients with AP.
2.3 Aims of the thesis

This thesis had two overall goals:

To develop a new classification of AP severity based on contemporary clinical needs and sound epidemiological grounds.

To provide meta-analytical and new RCT evidence to optimise nutritional management of patients with AP.

The specific aims pertinent to the first goal of the thesis were as follows:

1. To develop a conceptual framework for the new classification of AP severity (Chapter 3).
2. To validate a new category of severity that incorporates patients with extremely high mortality (Chapter 4).
3. To conduct a global survey of controversies pertinent to classifying the severity of AP (Chapter 5).
4. To propose a new classification of severity and its operational characteristics (Chapter 6).

The specific aims pertinent to the second goal of the thesis were as follows:

5. To determine the safety and efficacy of nasogastric tube feeding and compare the outcomes of nasogastric versus nasojejunal tube feeding in patients with AP (Chapter 7).
6. To develop a rationale for a randomised trial of early nasogastric tube feeding in patients with non-severe AP (Chapter 8).
7. To conduct the RCT of early nasogastric tube feeding versus a NBM regimen in patients with mild to moderate AP (Chapter 9).

8. To determine the optimal enteral nutrition formulation in patients with AP (Chapter 10).
PART I

NEW CLASSIFICATION OF ACUTE PANCREATITIS SEVERITY

AP has been known as a distinct clinical entity since the end of the 19th century, but its management is still characterised by an absence of specific treatments, despite extensive clinical and experimental research. In part this has stemmed from the limitations of the classifications for AP severity used so far, and these were discussed in the preceding chapter. It may well be that the perpetual use of classifications which were solely based on empiric description of severity has retarded progress in the field due to systematic misclassification in selecting patients for clinical trials, evaluating the effects of treatment, and comparing the inter-institutional data. As Albert Einstein said, “We cannot solve problems using the same kind of thinking we used when we created them”. If specific treatments for AP are to be identified, then fresh thinking in regards to classifying the severity of disease is needed.

An analogy can be drawn with the field of chemistry where classification schemes of the chemical elements were empirical for centuries until Dmitry Mendeleev suggested a sound scientific framework (the periodic law) to classify all then-known chemical elements and published the first version of the periodic table of the elements in 1869. He envisaged that the magnitude of the atomic weight determines the character of the element and that the elements exhibit recurring trends in properties if arranged according to their atomic weight. Apart from classifying all chemical elements on the basis of a meaningful concept, the invention of the periodic table contributed
significantly to progress in the field of chemistry by predicting accurately the presence of several then-unknown elements and questioning the atomic weights of some then-known elements (that could be measured only crudely at that time).

After several decades of deliberations, the time has come to develop a classification of AP severity on a sound evidential base. Part I (Chapters 3–6) of this thesis describes step-by-step the process of developing a new classification based on an epidemiologically sound and clinically meaningful concept of causal inference. Chapter 3 lays down the conceptual framework for the new classification of severity. Chapter 4 validates a new “critical” category of severity. Chapter 5 presents the opinions of leading pancreatologists with regard to topical questions pertinent to classifying the severity. Chapter 6 expounds the new determinant-based classification of severity and its operational characteristics.
Chapter 3

CONCEPTUAL FRAMEWORK FOR CLASSIFYING SEVERITY OF ACUTE PANCREATITIS

Several important questions have to be considered with regard to classifying the severity of AP. These relate to how the classification is best used, what determines the severity of AP, how determinants relate to each other, the time course of determinants, and how many categories make sense.

3.1 Use of classification

A truly useful classification of severity should be applicable to all patients with AP and reflect, through its categories, clinically meaningful changes in individual patients as they happen. This means that it should accurately classify individual patients at all times during the disease course rather than at the time of hospital discharge (as suggested by the Atlanta symposium and/or at an arbitrary time point such as 7 days after onset (as suggested in the latest revision of the Atlanta definitions). Repeated evaluation of the severity of individual patients is a fundamental principle in the management of AP. The clinical trajectory of patients reflects the dynamics of the disease and the response to treatment which in turn helps to foresee the outcome.
3.2 Determinants of severity

The literature is replete with studies investigating risk factors, prognostic factors, predictors, and markers of severity which are based on a bewildering array of underlying pathophysiologic processes in AP. Notably, these studies define “severity” of AP in quite disparate ways, and two recent systematic reviews have clearly indicated the magnitude of the problem\textsuperscript{112,130}. The study by Bollen and colleagues found that, among 297 articles identified, the definition of “severity” could include a wide range of variables, namely local and/or systemic complications (as defined by the Atlanta symposium), admission to an ICU, length of ICU or hospital stay, complications requiring medical or operative intervention, mortality, and other non-specified criteria.\textsuperscript{112} The search was limited to articles published between 1993 and 2006 (inclusive) and indexed in MEDLINE only. The study by Sigounas and colleagues found that, among 184 articles identified, the definition of “severity” included local and/or systemic complications (as defined by the Atlanta symposium), multiple factor prognostic scores (APACHE II $\geq 8$ and/or Ranson $\geq 3$), death, Japanese criteria of severity, OF, pancreatic necrosis, infected pancreatic necrosis, length of hospitalisation, ICU admission, and need for surgery.\textsuperscript{130} The search was limited to studies on non-routine biomarkers published between 1966 and 2009 (inclusive), indexed in MEDLINE only, and published in the English language. Altogether, while more than a dozen different factors have been used to describe disease severity, not all are considered a cause of severity.

It is argued that accurate classification of severity can only be achieved if it is based on factors that are causally associated with severity. While undoubtedly there are
studies in the literature that demonstrate a statistically significant association between all the factors mentioned above and the severity of AP, one should bear in mind that the majority of statistical associations are non-causal, which essentially means that the observed association between two variables might be due to other measured or unmeasured variables affecting the results. In particular, there are several different explanations for an observed association, including chance, bias, confounding, effect-cause, and cause-effect relationships. The first four of these are non-causal associations, and only the last, i.e., the cause-effect relationship, is a causal association. In other words, when seeking factors on which to base a classification of severity, it is important to use only those that have a causal association with severity. These factors are infection status of necrosis and OF, and they are termed “determinants” in clinical epidemiology.

There are two non-causal associations that warrant further comment, i.e., those of “confounding” and “effect-cause”, because they are often misunderstood. Confounding occurs when the association between two variables (an exposure and an outcome) is due to a third variable (the confounder). The important conditions are that the confounder must be causally related to the outcome and the confounder must be associated with the exposure, but not be an intermediary (Figure 3.1).
There are numerous examples in the AP literature where an association due to confounding is taken to be causal. An example of confounding would be when patients with extensive pancreatic necrosis are considered to be more likely to die.\textsuperscript{96,133} This is a true association but it is not causal, because it turns out that a third factor, namely infection of the necrosis, is associated with the extent of necrosis and is the cause of mortality in AP (Figure 3.2). Thus, while in general it is true that patients with extensive necrosis are at increased risk of death, it is not true that the extent of pancreatic necrosis is a cause of mortality.
Figure 3.2 Confounding effect of pancreatic infection in association between the extent of pancreatic necrosis and mortality in patients with acute pancreatitis

Footnote: solid line represents a causal association; dashed line represents a non-causal association; arrow represents the direction of association. Abbreviation: PN, pancreatic necrosis.

Similarly, it is often implied that SIRS is causally associated with mortality in AP. However, there is a third factor, namely OF, which is associated with SIRS and is the cause of mortality in AP (Figure 3.3). Thus, while in general it is true that patients with SIRS are at increased risk of death, it is not true that SIRS is a cause of mortality.
Another area of confusion is failure to understand that the effect-cause relationship does not infer causality. An example of this is when it is stated that patients with AP undergoing surgery have more severe disease. This is a true association but it is not causal because the need for surgery is a consequence of severity (in particular, IPN) and not the cause. Thus, while in general it is true that patients who undergo surgery are at increased risk of death, it is not true that the need for surgery is a cause of severity (Figure 3.4).
**Figure 3.4** Association between the need for surgery and the need for ICU admission and mortality in acute pancreatitis

**Footnote:** solid line represents a causal association; dashed line represents a non-causal association; arrow represents the direction of association. **Abbreviations:** POF, persistent organ failure; IPN, infected pancreatic necrosis; ICU, intensive care unit.

Similarly, it is often thought that patients admitted to ICU have severe disease.\textsuperscript{138–140} This is a true association but it is not causal because the need for ICU admission is a consequence of severity (in particular, persistent OF) and not the cause. Thus, while in general it is true that patients who need ICU admission are at increased risk of death, it is not true that the need for ICU admission is a cause of severity (Figure 3.4).
3.3 Interaction between determinants

There is little agreement about how local and systemic determinants relate to each other. Some authors state that infection causes OF\textsuperscript{95,141}, while others claim that OF causes pancreatic infection\textsuperscript{142,143}. However, it is also possible that there is an interaction between these two key determinants. This interaction is best understood as “effect modification”, which is when the effect of one determinant on an outcome varies by the presence or absence of another determinant (Figure 3.5).\textsuperscript{131} The following chapter (Chapter 4) will investigate whether the effect of pancreatic infection on the severity of AP depends on the presence or absence of OF, and vice versa.

**Figure 3.5** Schematic depiction of effect modification

**Footnote:** solid line represents a causal association; dotted line represents an effect modification (interaction); arrow represents the direction of association.
3.4  Time course of determinants

The importance of timing of OF and IPN is well recognised. While it is widely accepted that OF may be both an early (SIRS-driven) and late (IPN-driven) event in the natural course of AP, it is generally considered that IPN is a late event. However, this view is challenged by a body of evidence demonstrating that IPN also occurs early in some patients with AP.

The timing of development of IPN can be reliably examined because there are published series that include surgical operations performed during the first and second week. In 1986, Beger and colleagues published a prospective clinical study evaluating the bacteriological status of pancreatic necrosis in relation to timing of surgery for AP.\textsuperscript{110} Overall, 39\% (45/114) of the consecutive series of patients had a positive bacteriological culture of the debrided necrosis. Although pancreatic infection was most often detected after the second week, it is pertinent to note that 11\% and 29\% of the patients developed infected pancreatic necrosis within the first 7 and 14 days after onset of AP, respectively (Table 3.1). Another study, from the Warshaw group, looked back at 44 patients with proven IPN and demonstrated a similar incidence of early pancreatic infection, with 5\% and 28\% occurring in the first 7 and 14 days, respectively.\textsuperscript{144}
### Table 3.1 Timing of pancreatic infection in the referred clinical studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Patients with confirmed IPN (n)</th>
<th>Duration of disease at time of diagnosis of IPN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 1–7</td>
</tr>
<tr>
<td>Beger et al\textsuperscript{110}</td>
<td>Germany</td>
<td>45</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Gerzof et al\textsuperscript{145}</td>
<td>USA</td>
<td>36</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Rattner et al\textsuperscript{144}</td>
<td>USA</td>
<td>44</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Tsui et al\textsuperscript{146}</td>
<td>China</td>
<td>65</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Besselink et al\textsuperscript{147}</td>
<td>The Netherlands</td>
<td>98</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>288</td>
<td>21 (7%)</td>
</tr>
</tbody>
</table>

**Abbreviation:** IPN, infected pancreatic necrosis.
Further evidence regarding the timing of development of IPN comes from studies that evaluated the utility of fine-needle aspiration (FNA) for the diagnosis of pancreatic infection. The first rigorous study was reported in 1987 by Gerzof and colleagues who performed CT-guided percutaneous FNA and Gram staining in 60 patients with suspected pancreatic infection.\textsuperscript{145} Overall, 60\% (36/60) had pancreatic infection confirmed; 22\% (8/36) within 7 days of onset of AP and 56\% (20/36) within 14 days (Table 3.1). Similarly, in a study from Germany (1988–1996) on the utility of ultrasound-guided FNA in 98 patients with CT-proven pancreatic necrosis, it was shown that the overall incidence of IPN was 34\%.\textsuperscript{148} During the first week, 21\% (7/33) of patients had a positive FNA, and this was confirmed by bacteriological culture of the debrided necrosis.

Timing of diagnosis of IPN has also been specifically examined in two recent studies, both published in 2009.\textsuperscript{146,147} In a study from China (study period 2000–2008) there were 336 patients with predicted severe AP.\textsuperscript{146} Pancreatic infection was confirmed by FNA in 19\% (66/336) of the patients overall, and 25\% (16/66) of these patients had proven IPN within the first 14 days (Table 3.1). In a study from The Netherlands (study period 2004–2007) there were 154 patients with pancreatic necrosis.\textsuperscript{147} Pancreatic infection was confirmed in 64\% (98/154) of patients overall. In 5\% (5/98) of these patients, IPN was proven within the first 7 days and in 18\% (18/98) within the first 14 days (Table 3.1). These modern studies are in accordance with earlier studies which showed that IPN occurs early in a notable proportion of patients and thus should be captured by classification of severity whenever it occurs. Put another way, a classification system requiring that pancreatic infection is captured only late could overlook early IPN, and result in misclassification error.
3.5 Number of categories

The use of a binary classification of severity to assess a treatment response poses a fundamental problem. It is based on an implicit assumption that there is a linear relationship between severity of AP and treatment response, and this is depicted as the clustering of the two categories of severity, “mild” and “severe”, at each end of the line (Figure 3.6A). It is assumed that patients at the top end of the line benefit most from a treatment while patients at the bottom end of the line benefit least. However, this assumption is rather simplistic given that the relationship is probably better understood as bell-shaped with a limited treatment response possible at both ends of the severity spectrum (Figure 3.6B). Thus, patients between the two ends are most likely to respond to treatment. However, there is also a spectrum in the middle which is likely to represent a number of subgroups with clinically meaningful differences in response to treatment and in clinical outcomes. These subgroups ought to be distinguished by an accurate classification of severity.
Figure 3.6 Categories of severity in relation to a linear (A) and bell-shaped (B) assumption of efficacy of treatment in acute pancreatitis
Another likely advantage to more than two categories of severity is the ability to upstage or downstage severity during the course of disease. The ability to identify individual patients who move from one category to another is an endpoint that will prove useful in clinical trials as well as in tracking the clinical trajectory of patients.

Lastly, it is helpful to consider lessons from oncology in regards to the systems used to stage cancer. In bygone days, clinicians involved in the management of a patient with cancer used a binary approach to classification and merely sought to determine whether a patient had localised or metastatic disease. Today, it is possible and important to identify more than just two groups of patients. The multi-stage (I–IV) classification system based on factors that determine cancer survival (the primary tumour [T], regional nodal status [N], and distant metastases [M]) has proven to be useful in determining prognosis, aiding clinical decision-making, and for recruiting and reporting clinical trials. The universal adoption of this multi-stage classification has contributed to the successful evaluation and introduction of effective specific treatments for cancer.

3.6 Conclusion

Classifying the severity of AP should be based on actual determinants rather than descriptors of severity. Applying the evidence-based concept of causal inference reveals that the key determinants of severity in AP are infection status of pancreatic necrosis and OF. These determinants can occur together or separately, can potentially modulate the effect of the other, and can occur in either order and at any time during the course of AP in individual patients. A classification of severity that is applied
statically (e.g., on day 7 or on discharge) will not allow the determinants and treatment effects to be monitored dynamically. Categories in classification of severity should reflect groups with significantly and distinctly different outcomes.
Chapter 4

“CRITICAL” CATEGORY OF SEVERITY

Chapter 3 indicated that the traditional binary approach (“mild” and “severe”) to classifying the severity of AP is relatively crude and does not accurately reflect the real spectrum of patients with this disease. Two recent studies have proposed an intermediate category of severity, so-called “moderately severe” AP, which was principally constructed on the presence of local complications (as defined by the Atlanta symposium) but no systemic complications. These patients would have previously been classified as having “severe” AP. This chapter examines whether it is possible to distinguish another subgroup of patients amongst those who would have previously been classified as having “severe” AP, i.e., those at the severe end of the spectrum with both local and systemic complications.

4.1 Introduction

AP is a protean disease which varies locally from mild pancreatic oedema and inflammation to extensive infected pancreatic and peripancreatic necrosis, and systemically from a mild hypoxaemia to multiple OF. Factors influencing disease severity in AP continue to be the subject of debate. Fitz, at the end of the 19th century, believed that these factors were pancreatic haemorrhage and disseminated fat necrosis. A century later, the Atlanta classification stated that the presence of local pancreatic complications and extrapancreatic OF were factors of severity. More
recently it has been postulated that OF is the key factor of severity regardless of the presence or absence of local pancreatic complications.\textsuperscript{22,142}

It has also been appreciated that local pancreatic complications, such as fluid collections, pseudocysts, and necrosis, are not all equal contributors to disease severity. The widespread introduction of FNA of pancreatic tissue has helped to highlight the importance of infection, particularly IPN, as a key determinant of disease severity.\textsuperscript{94,95,141} However, studies that have examined the relationship between pancreatic infection and mortality are not all in agreement. Some have demonstrated a strong association between the infection status of pancreatic necrosis and mortality\textsuperscript{94,95,141}, while others have failed to do so\textsuperscript{133,143}. There may be a number of legitimate reasons for the lack of accord between these studies, including heterogeneous study populations of patients with and without OF and small study sample sizes.

4.2 Study aim

The aim of this study was to conduct a meta-analysis of published clinical studies to determine the influence of OF and IPN, both individually and combined, on mortality in patients with AP.
4.3 Methods

4.3.1 Study identification

Relevant publications were identified using electronic databases (MEDLINE, Scopus, and EMBASE) to search for studies published between January 1, 1993 (when the current Atlanta classification became available) and August 1, 2009, with no geographic or language restrictions. The search terms used were “acute pancreatitis”, “organ failure”, and “infection”. The search was limited to human adults. References cited in published original and review papers were searched to identify additional studies. An additional manual search was done using the abstracts of major gastroenterological meetings (Digestive Disease Week and United European Gastroenterology Week) from 2005 to 2009.

4.3.2 Study selection criteria

To be included, studies had to meet the following criteria:

1) A prospective and retrospective cohort design
2) A patient population with AP
3) Exposure
   - IPN versus no IPN in patients with OF; IPN had to be confirmed by a positive culture result from FNA, swab at the time of surgery, or culture from the removed necrosis
   - OF versus no OF (as defined by the authors of the primary studies) in patients with IPN
OF without IPN versus IPN without OF in patients with AP

4) In-hospital mortality as an outcome.

Wherever multiple publications of the same study population were available, the paper with the most complete and relevant set of data was chosen. Studies that assessed a specific prophylaxis or treatment were excluded.

4.3.3 Data abstraction

Full-text articles of the studies that met all the inclusion criteria were retrieved. Qualitative and quantitative information was abstracted using a standardised data collection form. Authors of studies published on AP that mentioned pancreatic infection or OF but did not provide data were contacted to request the data necessary to include them in the meta-analysis. All non-English papers were translated by native speakers who are experienced gastroenterologists or surgeons.

4.3.4 Quality assessment

Methodological quality was assessed using the Newcastle-Ottawa Scale. A quality score was calculated on the basis of the following components: selection of the study groups (0–4 points), quality of the adjustment for confounding (0–2 points), and ascertainment of the outcome of interest in the cohort (0–3 points). A higher score represented better methodological quality.
4.3.5 Statistical analysis

Relative risk (RR) of in-hospital mortality was used as the primary effect estimate in this meta-analysis. From the eligible studies that met the inclusion criteria, estimates of RR and the associated 95% CI were calculated using the Review Manager software (Version 5.0 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008)\textsuperscript{152}.

Pre-specified subgroup analyses were performed according to the number of failed organs (single versus multiple), definition of OF (according to the Atlanta classification versus others), indications for surgery (IPN only versus others), year of publication (arbitrarily, before 2007 versus on or after 2007), study type (prospective versus retrospective cohorts), study countries (United States and Western Europe versus other countries), and language of publication (English versus non-English). Pre-specified sensitivity analysis constrained to patients with pancreatic necrosis only (confirmed by CT) was conducted.

All meta-analyses appraised between-study heterogeneity using the Q measure for statistical significance and the $I^2$ measure for the amount of heterogeneity, with $p < 0.10$ being statistically significant and $I^2 > 25\%$ showing important heterogeneity. If there was no heterogeneity, a fixed-effects model based on the Mantel and Haenszel estimator was used; otherwise, a random-effect model based on the DerSimonian and Laird estimator was used.\textsuperscript{152} To assess the potential for publication bias, we performed the Begg’s test and the Harbord’s modified test for small-study effect, with $p < 0.05$ being statistically significant. The PRISMA (Preferred Reporting Items for Systematic
Reviews and Meta-Analyses) guidelines were used to report the results of this study.\textsuperscript{153}

4.4 Results

4.4.1 Study characteristics

From the initial literature search we identified and screened 513 abstracts (Figure 4.1). Sixty-one articles were considered of potential value and the full text was retrieved for detailed evaluation. Forty-seven of these 61 articles were subsequently excluded from the meta-analysis (42 did not satisfy the inclusion criteria, five were based on the same study populations). Fourteen original reports (nine prospective and five retrospective cohort studies) provided data to investigate the influence of OF and infection status of pancreatic necrosis on mortality.\textsuperscript{95,96,109,133,139,154–162} The included studies were published between 1997 and 2009 (Table 4.1). Seven studies were conducted in Europe\textsuperscript{95,139,156–159,162}, three in North America\textsuperscript{154,155,160}, two in Asia\textsuperscript{96,109}, and two in Central and Latin America\textsuperscript{133,161}. Eleven were written in the English language\textsuperscript{95,96,109,133,139,154,155,157,159,160,162}, one in Russian\textsuperscript{158}, one in Spanish\textsuperscript{161}, and one in Turkish\textsuperscript{156}. 
Figure 4.1 Flow diagram of the study selection process

- Potentially relevant publications identified (n = 513)
- Potentially appropriate studies to be included in systematic review (n = 61)
- Studies included in systematic review (n = 14)
- Studies excluded:
  - n = 452 – excluded after reading the abstract
  - n = 42 – did not satisfy the inclusion criteria
  - n = 5 – used the same study population as in the included study
Table 4.1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study design</th>
<th>All patients (n)</th>
<th>Patients with OF (n)</th>
<th>Patients with IPN (n)</th>
<th>Overall mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenner et al, 1997&lt;sup&gt;154&lt;/sup&gt;</td>
<td>USA</td>
<td>Retrospective</td>
<td>51</td>
<td>26 (51%)</td>
<td>18 (35%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Buchler et al, 2000&lt;sup&gt;155&lt;/sup&gt;</td>
<td>Switzerland</td>
<td>Prospective</td>
<td>204</td>
<td>74 (36%)</td>
<td>29 (14%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Le Mee et al, 2001&lt;sup&gt;139&lt;/sup&gt;</td>
<td>France</td>
<td>Prospective</td>
<td>43</td>
<td>43 (100%)</td>
<td>27 (63%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Perez et al, 2002&lt;sup&gt;155&lt;/sup&gt;</td>
<td>USA</td>
<td>Retrospective</td>
<td>99</td>
<td>51 (52%)</td>
<td>37 (37%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Garg et al, 2005&lt;sup&gt;156&lt;/sup&gt;</td>
<td>India</td>
<td>Prospective</td>
<td>104</td>
<td>37 (36%)</td>
<td>30 (29%)</td>
<td>24 (23%)</td>
</tr>
<tr>
<td>Remes-Troche et al, 2006&lt;sup&gt;133&lt;/sup&gt;</td>
<td>Mexico</td>
<td>Retrospective</td>
<td>165</td>
<td>49 (30%)</td>
<td>14 (8%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Tireli et al, 2006&lt;sup&gt;156&lt;/sup&gt;</td>
<td>Turkey</td>
<td>Prospective</td>
<td>38</td>
<td>14 (37%)</td>
<td>13 (34%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Rau et al, 2007&lt;sup&gt;157&lt;/sup&gt;</td>
<td>Europe</td>
<td>Prospective</td>
<td>104</td>
<td>68 (65%)</td>
<td>17 (16%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Sharma et al, 2007&lt;sup&gt;159&lt;/sup&gt;</td>
<td>India</td>
<td>Prospective</td>
<td>282</td>
<td>94 (33%)</td>
<td>57 (20%)</td>
<td>57 (20%)</td>
</tr>
<tr>
<td>Lutfarakhmanov et al, 2007&lt;sup&gt;138&lt;/sup&gt;</td>
<td>Russia</td>
<td>Prospective</td>
<td>72</td>
<td>39 (54%)</td>
<td>26 (36%)</td>
<td>17 (24%)</td>
</tr>
<tr>
<td>Lytras et al, 2008&lt;sup&gt;159&lt;/sup&gt;</td>
<td>Greece</td>
<td>Prospective</td>
<td>64</td>
<td>33 (52%)</td>
<td>17 (27%)</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Rocha et al, 2009&lt;sup&gt;160&lt;/sup&gt;</td>
<td>India</td>
<td>Retrospective</td>
<td>64</td>
<td>36 (56%)</td>
<td>15 (23%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Pellegrini et al, 2009&lt;sup&gt;161&lt;/sup&gt;</td>
<td>Argentina</td>
<td>Retrospective</td>
<td>97</td>
<td>12 (12%)</td>
<td>4 (4%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Radenkovich et al, 2009&lt;sup&gt;162&lt;/sup&gt;</td>
<td>Serbia</td>
<td>Prospective</td>
<td>91</td>
<td>24 (26%)</td>
<td>10 (11%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1478</td>
<td>600 (40%)</td>
<td>314 (21%)</td>
<td>191 (13%)</td>
</tr>
</tbody>
</table>

Footnote: International multicentre trial from Germany, Finland, Switzerland, and Italy. Abbreviations: OF, organ failure; IPN, infected pancreatic necrosis.
4.4.2 Methodological quality

The methodological quality of the included studies is presented in Table 4.2.

**Table 4.2** Quality assessment of included studies based on the Newcastle-Ottawa Scale

<table>
<thead>
<tr>
<th>Reference</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenner et al, 1997^154</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Buchler et al, 2000^95</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Le Mee et al, 2001^139</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Perez et al, 2002^155</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Garg et al, 2005^96</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Remes-Troche et al, 2006^133</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tireli et al, 2006^130</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Rau et al, 2007^157</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Sharma et al, 2007^109</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lutfarakhmanov et al, 2007^158</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lytras et al, 2008^159</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rocha et al, 2009^100</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pellegrini et al, 2009^161</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Radenkovich et al, 2009^162</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
4.4.3 Publication bias assessment

There was no statistical evidence of publication bias among the included studies using Begg’s test (p = 0.27) and Harbord’s test (p = 0.35).

4.4.4 Overall patient characteristics

The 14 studies encompassed a total of 1478 patients with AP, including 876 patients with confirmed pancreatic necrosis. The prevalence of OF was 40% (600 of 1478 patients) and the prevalence of IPN was 21% (314 of 1478 patients) as shown in Table 4.1. The overall mortality was 13% (191 of 1478 patients), of which 30% (179 of 600 patients) was in all patients with OF regardless of the presence or absence of IPN, and 32% (102 of 314 patients) in all patients with IPN regardless of the presence or absence of OF.

4.4.5 Influence of pancreatic infection on mortality in patients with organ failure

The 14 studies provided data for determining the relationship between presence or absence of pancreatic infection and mortality in patients with OF. Mortality was 43% (92 of 213) in patients with OF and confirmed IPN, as opposed to only 22% (87 of 387) in those with OF and no IPN. The presence of IPN was associated with a significantly increased risk of death in patients with OF (RR 1.94; 95% CI 1.32–2.85; p = 0.0007, Figure 4.2). A significant heterogeneity was observed (p = 0.02; $I^2 = 48\%$). This heterogeneity was eliminated when a pre-specified
sensitivity analysis of only patients with confirmed pancreatic necrosis was conducted (p = 0.50; I² = 0). Infected, when compared with sterile, pancreatic necrosis was associated with a significantly increased risk of death (RR 1.84; 95% CI 1.40–2.41; p < 0.0001).

The pooled estimate was remarkably robust; omission of a primary study resulted in a range of RR between 1.72 (95% CI 1.31–2.26) after omission of the study by Lytras and colleagues¹⁵⁹ and 1.99 (95% CI 1.48–2.68) after omission of the study by Lutfarakhmanov and colleagues¹⁵⁸. In the pre-specified subgroup analyses, the effect did not appear to depend on the number of failed distant organs, definition of OF, indications for surgery, type of study, year of publication, or study setting. At the same time, when stratifying for language of publication, risk estimate was statistically significant only in papers published in English as opposed to non-English language.

Figure 4.2 Forest plot for mortality associated with infected pancreatic necrosis compared with no infected pancreatic necrosis in patients with organ failure.
4.4.6 Influence of organ failure on mortality in patients with infected pancreatic necrosis

Ten studies provided data for determining the relationship between the presence or absence of OF and mortality in patients with IPN.\textsuperscript{95,96,109,133,154–157,159,160} Mortality was 11\% (10 of 93) in patients with confirmed IPN but no OF. Figure 4.3 shows the forest plot with the pooled estimate for risk of death in patients with IPN and OF compared with those with IPN and no OF. The OF group was associated with a significantly increased risk of death (RR 2.65; 95\% CI 1.30–5.40; p = 0.0007). Minimal heterogeneity was observed ($I^2 = 35\%$). The pooled estimate was robust; omission of a primary study resulted in a range of RR between 2.26 (95\% CI 1.17–4.37) after omission of the study by Garg and colleagues\textsuperscript{96} and 3.22 (95\% CI 1.23–8.41) after omission of the study by Sharma and colleagues\textsuperscript{109}. The pre-specified subgroup analyses did not reveal a statistically significant difference between the risk estimates.

![Forest plot for mortality associated with organ failure compared with no failure in patients with infected pancreatic necrosis](image)

**Figure 4.3** Forest plot for mortality associated with organ failure compared with no failure in patients with infected pancreatic necrosis
4.4.7 Influence of organ failure versus pancreatic infection on mortality in patients with acute pancreatitis

Ten studies provided data to compare mortality of patients with OF and no IPN versus those with IPN and no OF. Figure 4.4 shows the forest plot with no statistically significant difference in the risk of death between these two groups (RR 1.44; 95% CI 0.53–3.93). Moderate heterogeneity was observed ($I^2 = 51\%$). Sensitivity analysis limited to patients with confirmed pancreatic necrosis also did not reveal a significant difference between the groups (RR 1.66; 95% CI 0.68–4.04). The pre-specified subgroup analyses did not show a statistically significant difference between the risk estimates.

**Figure 4.4** Forest plot for mortality associated with organ failure without infected pancreatic necrosis, compared with that of infected pancreatic necrosis without organ failure, in patients with acute pancreatitis
4.5  Discussion

This is the first study to have specifically investigated the influence of OF and IPN, both individually and combined, on the mortality of patients with AP. It was found that the presence of OF regardless of the presence or absence of IPN led to mortality in 30% of patients and that the presence of IPN regardless of the presence or absence of OF led to mortality in 32% of patients. Notably, the risk of death was two times higher in patients with both OF and IPN in comparison with patients with OF and no IPN and in comparison with patients with IPN and no OF. These findings have both theoretical and practical importance.

From a theoretical perspective, this study sheds further light on the relationship between OF and IPN in patients with AP. Several studies over the last decade have found that patients with IPN develop OF more often than those with sterile pancreatic necrosis, and suggested that infection of pancreatic necrosis is a risk factor for OF and a major determinant of severity in AP. By contrast, a number of studies have also found the converse, i.e., that OF is a risk factor for development of IPN and a major determinant of severity. Both these approaches are simplistic, making the assumption that there is a single major determinant of severity. Importantly, an interaction between determinants, when the two variables modify the effect of each other with regard to the outcome, has never been properly investigated in the setting of AP. This study indicates that OF and IPN accentuate the effect of each other on mortality, suggesting that there is a positive interaction (synergism) between OF and pancreatic infection in patients with AP.
From a practical perspective, this study identifies a subgroup of AP patients with both OF and IPN who have a substantially higher mortality. This finding is consistent with the original Atlanta definitions acknowledging that the presence of OF and/or IPN contributes to severity. The present study takes this further by demonstrating that both OF and IPN are equivalent determinants of severity, because their presence is associated with a mortality rate of 30% and 32%, respectively. Organ failure and IPN present together is associated with more severe disease and an even higher mortality rate (43%). This subgroup comprises a quarter of patients with acute necrotising pancreatitis (24%, 213 of 876 patients in the present study) and has nearly double the mortality of patients with OF and no IPN. This finding provides strong justification for the introduction of a new category of severity, with this worst prognosis group being termed “critical” AP.

The Atlanta classification defined two categories of patients with AP, those with “mild” and “severe” disease. There has been the recent suggestion for a third category of patients. This “moderate” category of AP includes patients with local non-infectious complications and those with transient OF. Based on the presence of local (absence, sterile, infectious) and systemic (absence, transient, persistent) complications of AP and the possibility of their interaction, there are now four categories of severity in AP which can be defined robustly, have a strong epidemiological basis to support them and, most importantly, have clinical relevance (Table 4.3). Use of these categories has a potential to improve clinical assessment of individual patients during the course of AP, communication between caregivers, and comparison between groups in clinical studies.
Table 4.3 Classification and definitions of four categories for severity of acute pancreatitis

<table>
<thead>
<tr>
<th>Severity category</th>
<th>Local determinant</th>
<th>Systemic determinant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>No pancreatic complications and No organ failure</td>
<td></td>
</tr>
<tr>
<td>Moderate*</td>
<td>Sterile pancreatic complications or Transient organ failure</td>
<td></td>
</tr>
<tr>
<td>Severe*</td>
<td>Infectious pancreatic complications or Persistent organ failure</td>
<td></td>
</tr>
<tr>
<td>Critical</td>
<td>Infectious pancreatic complications and Persistent organ failure</td>
<td></td>
</tr>
</tbody>
</table>

**Footnote:** *Severity is graded on the basis of more severe local or systemic complication (e.g., sterile pancreatic necrosis without organ failure has to be graded as “moderate”; sterile pancreatic necrosis with persistent organ failure has to be graded as “severe”).*
4.6 **Strengths**

The present study has several important strengths. To our knowledge, this is the first meta-analysis of major determinants of mortality in patients with AP. The use of the meta-analytic technique allows an increase in the statistical power, which is of paramount importance taking into account that the prevalence of IPN and OF in patients with AP is relatively low. In fact, most primary studies had inadequate statistical power to estimate all the determinants of mortality. This study employed explicit eligibility criteria and a comprehensive search in three major electronic databases as well as in the grey literature with no language restriction. The majority of the included studies had adequate overall methodological quality according to the Newcastle-Ottawa scale. The effect was very consistent over all published studies, and the pooled estimates had narrow CIs. Furthermore, we performed a pre-specified sensitivity analysis constrained to patients with confirmed necrotising pancreatitis only and a number of subgroup analyses to ensure that certain characteristics of the primary studies had not influenced the pooled estimates.

4.7 **Limitations**

There are a number of possible limitations to this study, and these need to be acknowledged. Firstly, the analysis was based solely on observational studies that might be prone to confounding. While, in general, confounders are best addressed by RCTs, studies of this design would not be able to address a research question related to the natural course of the disease, particularly one related to the relationship between OF and pancreatic infection in AP.
Secondly, there are potential problems in relation to the different definitions of OF and the different indications for surgical intervention across the primary studies. We addressed this issue by means of pre-specified subgroup analyses, which confirmed the robustness of our findings regardless of the definition of OF used and indications for surgery.

Thirdly, in recent years it has been appreciated that the dynamic nature of OF is of importance, because persistent OF has a worse prognosis than transient OF. Unfortunately, only a few of the primary studies included data on the dynamic nature of OF and thus it was not possible to analyze this aspect. However, it is worth mentioning that the biggest study to date on this topic reported a 35% (36 of 103 patients) mortality rate in patients who developed persistent OF, but did not report on the influence of pancreatic infection. This is very consistent with the 30% (179 of 600 patients) mortality in patients with OF regardless of the presence or absence of pancreatic infection in the present study. Importantly, having stratified these patients according to the infection status of pancreatic necrosis, we found a mortality rate of 43% in patients with OF and IPN compared with 22% in patients with OF and no IPN.

Fourthly, we were not able to investigate the effect of “early” versus “late” OF in the present study, because the data were not available. However, to the best of our knowledge, no studies demonstrated that early OF is more ominous than late OF in patients with AP. The studies on early AP will be discussed in detail in Chapter 6.
Lastly, as is always the case in meta-analyses, the results are susceptible to publication bias, such that studies showing a significant effect are more likely to be published. We believe this bias is minimal because the relationship between infection status of pancreatic necrosis and the presence or absence of OF was not the primary outcome of interest in any of the studies in this meta-analysis. Moreover, two different statistical tests used to examine the issue of publication bias were performed and revealed no statistical evidence of significant publication bias.

4.8 Conclusion

This study has demonstrated that OF and IPN are independent and equivalent determinants of mortality in patients with AP. There is a statistically significant two-fold increase in the risk of death when both OF and IPN are present. This finding highlights the positive interaction between OF and IPN as determinants of severity in AP. It also provides justification for the inclusion of the new category of “critical” AP in classifying the severity of this disease.
Chapter 5

INTERNATIONAL SURVEY OF CONTROVERSIES IN CLASSIFYING

SEVERITY OF ACUTE PANCREATITIS

Chapter 4 clarified the relationship between local and systemic determinants of severity by demonstrating the presence and strength of an interaction between these two key determinants. Coupled with a wealth of literature demonstrating the prognostically important attributes of local (absent, sterile or infected [peri] pancreatic necrosis) and systemic (absent, transient or persistent OF) determinants, this provides a sound rationale for four categories of severity in AP, i.e., “mild”, “moderate”, “severe”, and “critical”. This chapter presents the results of the first global survey of leading pancreatologists to seek their opinion about the notion of four categories of severity and other issues related to classifying the severity of AP for which there remains a lack of evidence or that is available but inconsistent.

5.1 Introduction

Classifying the severity of AP is an integral part of clinical decision-making and research. Several important advances have been made recently in this area. These include appreciation of determinants of severity rather than descriptors of severity, recognition of interaction between the determinants, and introduction of new and clinically valid categories of AP. The adequacy of the traditional binary
approach to classifying severity has been questioned, and the notion of a new four-
category classification scheme has been developed based on these advances.

At the same time, there are still some controversial issues related to the classification
of severity. These may be due to a lack of published studies or the inconsistent results
of published studies. The controversies relate to the optimal definition of pancreatic
necrosis and OF, the prognostic significance of certain local collections, and the
number, timing and duration of OF.

5.2 Study aim

The aim of this study was to capture the opinions of the global pancreatology
community about the controversies relating to classifying the severity of AP.

5.3 Methods

The corresponding authors of all articles on AP published during a 5-year period
(2006–2010) were identified through MEDLINE. The search was limited to studies in
humans. No language restrictions were applied. The full texts were retrieved if the
email address was not available in the abstract. Each corresponding author was entered
into the database. If several email addresses were found, the most recent one was
selected.
The online survey was created using a commercial service (SurveyMonkey™) and beta-tested before distribution to the pancreatologists. It contained four sections (personal information, local determinants of severity, systemic determinants of severity, and classification of severity) as well as a free-text section for additional comments on the subject of the survey (Appendix 1). The language of the survey was English. The pancreatologists were contacted by email and asked to participate in an online survey. One reminder was sent 2 weeks after the initial invitation. The survey was closed 4 weeks after the initial invitation. The North Island X Ethics Committee (Auckland, New Zealand) granted exemption for this study.

All survey responses were collected and tabulated by SurveyMonkey. Statistical analysis was performed using SPSS statistical software (version 18, SPSS Inc, Chicago, IL). The significance of the relationship between categorical variables was examined using the Pearson $\chi^2$ test or analysis of variance, as appropriate. P values less than 0.05 were considered statistically significant. Subgroup analyses according to the respondents’ specialty (surgery, gastroenterology, and other) and sensitivity analyses constrained to an “expert panel”, arbitrarily defined as those who authored 10 or more papers pertinent to acute pancreatitis over the last 5 years (i.e. 2 papers per year on average), were conducted.

5.4 Results

A total of 576 unique corresponding authors of articles related to clinical aspects of AP were identified. Email invitations were sent to all the authors from 55 countries and 528 of them were delivered (36 bounced, 12 blocked). Responses were received
from 244 authors representing 50 countries. Four authors opted out, leaving 240 (45%) responses from 49 (89%) countries for analysis (Table 5.1).

**Table 5.1** List of participating countries in the survey

<table>
<thead>
<tr>
<th>Country</th>
<th>Response count</th>
<th>Response percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>37</td>
<td>15.42%</td>
</tr>
<tr>
<td>Japan</td>
<td>16</td>
<td>6.67%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>16</td>
<td>6.67%</td>
</tr>
<tr>
<td>Germany</td>
<td>15</td>
<td>6.25%</td>
</tr>
<tr>
<td>Spain</td>
<td>13</td>
<td>5.42%</td>
</tr>
<tr>
<td>Turkey</td>
<td>13</td>
<td>5.42%</td>
</tr>
<tr>
<td>Italy</td>
<td>11</td>
<td>4.58%</td>
</tr>
<tr>
<td>India</td>
<td>10</td>
<td>4.17%</td>
</tr>
<tr>
<td>Brazil</td>
<td>7</td>
<td>2.92%</td>
</tr>
<tr>
<td>Finland</td>
<td>7</td>
<td>2.92%</td>
</tr>
<tr>
<td>Australia</td>
<td>6</td>
<td>2.50%</td>
</tr>
<tr>
<td>China</td>
<td>6</td>
<td>2.50%</td>
</tr>
<tr>
<td>Netherlands</td>
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<tr>
<td>France</td>
<td>5</td>
<td>2.08%</td>
</tr>
<tr>
<td>Greece</td>
<td>5</td>
<td>2.08%</td>
</tr>
<tr>
<td>Romania</td>
<td>5</td>
<td>2.08%</td>
</tr>
<tr>
<td>Argentina</td>
<td>4</td>
<td>1.67%</td>
</tr>
<tr>
<td>Denmark</td>
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<td>1.67%</td>
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<tr>
<td>Hungary</td>
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<td>Slovakia</td>
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<tr>
<td>Austria</td>
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</tr>
<tr>
<td>Canada</td>
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<td>1.25%</td>
</tr>
<tr>
<td>Mexico</td>
<td>3</td>
<td>1.25%</td>
</tr>
<tr>
<td>Sweden</td>
<td>3</td>
<td>1.25%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>3</td>
<td>1.25%</td>
</tr>
<tr>
<td>Belgium</td>
<td>2</td>
<td>0.83%</td>
</tr>
<tr>
<td>Israel</td>
<td>2</td>
<td>0.83%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2</td>
<td>0.83%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>2</td>
<td>0.83%</td>
</tr>
<tr>
<td>Peru</td>
<td>2</td>
<td>0.83%</td>
</tr>
<tr>
<td>Poland</td>
<td>2</td>
<td>0.83%</td>
</tr>
<tr>
<td>Russia</td>
<td>2</td>
<td>0.83%</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Croatia</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Egypt</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Iran</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Latvia</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Lithuania</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Norway</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Philippines</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Serbia</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Slovenia</td>
<td>1</td>
<td>0.42%</td>
</tr>
</tbody>
</table>
5.4.1 Characteristics of respondents

The respondents came from all of the inhabited continents (Figure 5.1), i.e., 120 (50%) from Europe, 54 (22%) from Asia, 43 (18%) from North America, 14 (6%) from South America, eight (3%) from Australia, and one (0.4%) from Africa. The majority of respondents were from the United States, Japan, and the United Kingdom (Table 5.1). The specialties of the respondents were surgery (n = 107, 45%), gastroenterology (85, 35%), and other (48, 20%). The case load (average number of patients managed with AP per year) was more than 50 patients for 60 (25%) respondents, between 20 and 50 patients for 95 (39%) respondents, and less than 20 patients for 87 (36%) respondents. The respondents authored a median of 4 (range 1-43) papers on acute pancreatitis in peer-reviewed journals over the last 5 years; 63 respondents authored 10 or more papers and were considered as the “expert panel”.

<table>
<thead>
<tr>
<th>Country</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Thailand</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Ukraine</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Uruguay</td>
<td>1</td>
<td>0.42%</td>
</tr>
<tr>
<td>Venezuela</td>
<td>1</td>
<td>0.42%</td>
</tr>
</tbody>
</table>
Figure 5.1 Geographic distribution of respondents in the survey
5.4.2 Definition of local determinants of severity

i) Pancreatic and peripancreatic necrosis

The diagnosis of pancreatic necrosis would be made if there was any detectable pancreatic hypoperfusion on contrast-enhanced CT by 74 (35%) respondents. For the remaining respondents, the diagnosis of pancreatic necrosis would require at least 5% of pancreatic hypoperfusion by four (2%) of respondents, at least 10% by 22 (10%), at least 20% by 46 (22%) and at least 30% by 65 (31%). In a subgroup analysis, there was a significant difference between the opinions of gastroenterologists and others (p = 0.04), but not between surgeons and gastroenterologists or surgeons and others (Table 5.2). Almost half of the respondents (n = 105, 49%) stated that sterile pancreatic necrosis alone is, in general, associated with a worse outcome than sterile peripancreatic necrosis alone, 90 (43%) of respondents considered it to be associated with the same or better outcome, and 17 (8%) did not have an opinion. In a subgroup analysis, there was a significant difference between the opinions of surgeons and others (p = 0.03), but not for the other comparisons (Table 5.2).
Table 5.2 Subgroup analysis according to the responders’ specialty

<table>
<thead>
<tr>
<th>Question</th>
<th>Surgery (S)</th>
<th>Gastroenterology (G)</th>
<th>Other clinicians (O)</th>
<th>Pearson Chi-square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosing of pancreatic necrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30%</td>
<td>35</td>
<td>27</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20%</td>
<td>30</td>
<td>28</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10%</td>
<td>20</td>
<td>17</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5%</td>
<td>12</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile pancreatic and peripancreatic necrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic necrosis worse</td>
<td>47</td>
<td>41</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similar or peripancreatic worse</td>
<td>47</td>
<td>30</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No opinion</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition of a single organ failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A threshold</td>
<td>35</td>
<td>46</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A scoring system</td>
<td>63</td>
<td>31</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition of persistent organ failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 24-hour periods or more</td>
<td>44</td>
<td>45</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 24-hour periods or more</td>
<td>41</td>
<td>23</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 24-hour periods or more</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 24-hour periods or more</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition of multiple organ failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 systems or more</td>
<td>76</td>
<td>64</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 systems or more</td>
<td>22</td>
<td>12</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 systems or more</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support of a binary approach to classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>12</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>65</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support of the four-category classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>82</td>
<td>68</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>9</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maxim S Petrov - 75 - December 2011
ii) Sterile pancreatic collections

The presence of a well defined wall associated with a pancreatic collection was considered to be associated with a worse outcome by 85 (51%) respondents compared with 82 (49%) who considered that the absence of a well defined wall was associated with worse outcomes (p = 0.81). There was no statistically significant difference in opinions between the specialties (p = 0.32). Collections containing fluid and necrosum were considered to be associated with a worse outcome by 124 (74%) respondents compared with 43 (26%) respondents who considered that fluid-only collections were associated with worse outcomes (p < 0.001). There was no statistically significant difference between the specialties (p = 0.31). Table 5.3 gives the perceived prognostic significance of the four possible pancreatic collections. Twenty-two (10.4%) respondents felt that none of these are associated with severity and 23 (10.9%) did not offer an opinion.

Table 5.3 Perceived significance of sterile pancreatic collections in classifying the severity of acute pancreatitis

<table>
<thead>
<tr>
<th>Content</th>
<th>Definable wall†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Fluid and necrosum</td>
<td>65 (39%)</td>
<td>101 (60%)</td>
</tr>
<tr>
<td>Fluid only</td>
<td>35 (21%)</td>
<td>42 (25%)</td>
</tr>
</tbody>
</table>

Footnote: †Multiple answers were permitted
iii) Infected pancreatic collections

The overwhelming majority of respondents (n = 169, 80%) stated that infected pancreatic collections containing fluid and necrosum, with or without a well defined wall, are associated with a severity similar to infected pancreatic necrosis, while 16 (8%) stated that only collections with a well defined wall are associated with severity. Fifteen (7%) stated neither of these and 11 (5%) did not have an opinion.

5.4.3 Definition of systemic determinants of severity

The definition of OF using a multi-dimensioned scoring system (e.g., Sepsis-related Organ Failure Assessment [SOFA] or Multiple Organ Dysfunction) was preferred by 106 (55%) respondents, compared with 95 (45%) who preferred using a defined threshold for each separate organ system. There was a significant difference between surgeons who preferred the scoring systems and gastroenterologists who preferred using individual thresholds (p < 0.007), as shown in Table 5.2. Figure 5.2 demonstrates that renal, respiratory and cardiovascular systems were considered important.

With respect to the definition of multiple OF, 168 (80%) respondents indicated that “2 or more” organ systems were required compared with 43 (20%) who considered that at least three organ systems were required before the term “multiple organ failure” should be used. There were no statistically significant differences in opinions between the specialties (Table 5.2).
The definition of persistent OF was considered to be failure of the same system during at least two consecutive 24-hour periods by 111 (53%) respondents, during at least three consecutive 24-hour periods by 70 (33%), at least four consecutive 24-hour periods by 11 (5%), and at least five consecutive 24-hour periods by 18 (9%). In a subgroup analysis, there was a significant difference between the opinions of surgeons and others (p = 0.002), but not with the other comparisons (Table 5.2).

5.4.4 Classification of severity

There was very strong support for a classification of AP severity that included more than two categories (“mild” and “severe”) by 169 (81%) respondents, and only 40 (19%) respondents considered that a binary approach to the classification is adequate. There was no statistically significant difference in opinions between the specialties (Table 5.2). The concept of a determinant-based classification of severity (“mild”, “moderate”, “severe”, and “critical”) was supported by 183 (88%) respondents and not supported by 26 (12%) respondents. There was no statistically significant difference in opinions between the specialties (Table 5.2). Figure 5.2 demonstrates the perceived usefulness of the new classification system in clinical practice and clinical research. The new four-category classification of severity was considered useful for clinical practice by 188 (90%) respondents and useful for clinical research by 191 (91%) respondents.

Sensitivity analysis revealed that the expert panel did not significantly differ from the group overall in terms of all the studied questions.
Figure 5.2 Usefulness of the four-category classification of severity in clinical practice (A) and research (B)
5.5 Discussion

This is the first global survey in the field of AP. All the previous published surveys were constrained to a certain geographic area.\textsuperscript{169–171} While members of professional societies/associations were targeted in other surveys, this survey targets the known active contributors to the field. It has benchmarked current opinions from leading pancreatologists with regard to the definitions of local and systemic determinants of severity and classifying the severity of AP. Importantly, the survey focused on controversial issues only, i.e., questions critical for uniform classifying of severity worldwide but either not addressed in published studies or addressed but yielded inconsistent results.

With respect to local determinants, the survey has shown that peripancreatic necrosis and pancreatic necrosis are considered to be equivalent in regards to severity. This is important because a growing number of publications in recent years have reported on the prognostic importance of peripancreatic necrosis but its place in classifying the severity of AP has not been established yet, nor how reliable is the diagnosis of this entity.\textsuperscript{101,103,104,172} Another important finding of the survey is that the content of pancreatic collections but not the presence or absence of a definable wall is considered to be associated with severity. In particular, a pancreatic collection without a well defined wall that contains fluid and necrosis (sometimes referred to in the literature as “acute necrotic collection”) and a pancreatic collection with a well defined wall that contain fluid and necrosis (sometimes referred to in the literature as “walled-off necrosis”) are considered to be associated with severity. At the same time, peripancreatic fluid collections without a wall or necrosis (sometimes referred to in the
literature as “acute peripancreatic fluid”) and peripancreatic fluid collection with a well defined wall that does not contain necrosis (sometimes referred to in the literature as “pancreatic pseudocyst”) are not considered to be associated with severity. These distinctions are important because a new set of morphological terms has been proposed on the basis of good agreement between clinicians and radiologists with regard to interpretation of CT scans. While this is likely to provide more reliable reporting of CT findings, it is important to note that this does not imply that all these entities have prognostic significance. It is best to use prognostically important factors only for the purpose of classifying the severity of AP.

With respect to systemic determinants, the survey has shown that failure of renal, respiratory, and cardiovascular systems are of much more prognostic importance than failure of other organ systems, which is consistent with the recent, but not earlier, literature. The recent literature also suggests that OF is better defined on the basis of a multi-dimensional scoring system than a defined threshold for each separate organ system. However, this view was not supported by nearly half of the respondents, possibly indicating some practical concerns regarding the use of scoring systems on a daily basis, especially outside the ICU.

It was notable that less than 20% of the respondents considered that a binary approach to the classification of severity (“mild” and “severe”) was adequate for modern clinical practice and research. Clinicians recognise that the “severe” category contains subgroups of patients with distinct clinical outcomes. There are patients with transient OF or sterile necrosis that have a very low risk of mortality. In contrast, there are patients with IPN and OF who have a very high risk of mortality. It
makes little sense to combine these groups, labelling them all as having “severe” AP. Clinical experience, backed by sound data, exposes the impoverished two-category approach to classification. It is also striking that more than 80% of respondents considered the four-category classification of severity useful both for clinical practice and clinical research.

5.6 Limitations

There are several possible limitations to this study. The survey does not include the opinions of all pancreatologists in the world. Not all would be identified by the method employed in this research, not all opinion leaders were designated as corresponding authors, and half of those who received the survey did not respond. Nevertheless, there was an excellent response rate for this type of study (45% of authors representing 49 countries [89% of the countries invited]), and this compares favourably with the average 10%–20% author response rate and 40%–50% of invited author country response rate in contemporary worldwide online surveys of medical professionals.\textsuperscript{169,170,178–182} The approach taken was maximally objective, in that the published pancreatologists were invited to participate regardless of country of residence, language of publication, and affiliation with a professional body. However, it is acknowledged that, given that the survey was distributed in English only, it does not incorporate the opinions of pancreatologists who are not comfortable responding in this language. In particular, there were many articles on AP from China, but only a few pancreatologists from that country participated in the survey. It is also acknowledged that some corresponding authors might be relatively junior members of
the team, though the corresponding author was the senior author in the majority of cases.

5.7 Conclusion

This international survey of pancreatologists has yielded a valuable insight into the issues and definitions relating to classifying the severity of AP. It has highlighted both the areas of general agreement and where there is lack of consensus and priority areas for further clinical studies. The concept of a determinant-based classification comprising four categories of severity was supported by the overwhelming majority of pancreatologists who participated in the survey. The results of the survey will also assist the development of comprehensive and uniform definitions of determinants of severity.
Chapter 6

DETERMINANT-BASED CLASSIFICATION OF ACUTE PANCREATITIS SEVERITY

Chapters 3, 4, and 5 have laid down a scientific foundation for the new classification of severity. This chapter provides operational characteristics of the new classification, which include comprehensive definitions of determinants and categories of severity, and their rationale.

6.1 Introduction

Accurate classification of AP severity is important in both clinical practice and research. In clinical practice it is valuable to define severity, track the course, and support decision-making. In clinical research it is valuable to define criteria for recruitment, allowing valid comparisons between study groups. For more than a century, severity of AP has been classified as either “mild” or “severe” but defined in disparate ways.\textsuperscript{15,19,183,184} Recently, the limitations of using this dichotomous arrangement have become apparent because those considered to have severe disease comprise subgroups with very different outcomes. These subgroups include patients at higher risk of mortality due to persistent rather than transient OF, those without OF who are at higher risk of morbidity due to necrotising rather than interstitial
pancreatitis, and those with prohibitive mortality when IPN and persistent OF are both present rather than either alone.\textsuperscript{150,151,177,185,186}

The intention in this thesis has been to derive a classification of severity that is evidence-based, easy to use, with robust and uniform definitions, clinically meaningful, and also valuable in the research setting. It is considered that a classification of severity should be based on the actual key determinants of severity, rather than on descriptors of severity (discussed in more detail in Chapter 3). Given that AP evolves over time and that clinical events can occur in any order on any day, a classification of severity should be applicable at any time point.

The development of the determinant-based classification of AP severity has involved three stages. The first stage was recognising the limits of previous classifications, the proposal for “moderate” and “critical” categories, and proposal of a new classification.\textsuperscript{91,100,101,112,150,151,185} The second stage was a global survey of 576 leading pancreatologists from 55 countries to obtain expert opinion regarding the classification and its definitions (presented in Chapter 5). Notably, 81% of respondents indicated that a dichotomous approach to classification was not adequate for modern clinical practice and research. Furthermore, 88% of respondents supported the conceptual approach to the new classification. The third stage was convening a symposium during the World Congress of the International Association of Pancreatology (Kochi, India, February 2011) to discuss further the proposed classification and seek accord on the definitions. The programme of the symposium is presented in Appendix 2.
6.2 Determinants of severity

The classification is based on factors that are causally associated with severity. These factors are called “determinants”, and include both local and systemic determinants.

6.2.1 Local determinant

The local determinant of severity is necrosis of the pancreas and/or peripancreatic tissue. This is covered by the term (peri)pancreatic necrosis.

Definitions

- (Peri)pancreatic necrosis is non-viable tissue located in the pancreas alone, in the pancreas and peripancreatic tissues, or in peripancreatic tissues alone. It can be solid or semisolid (partially liquefied) and is without a radiologically defined wall.
- Sterile (peri)pancreatic necrosis is the absence of proven infection in necrosis.
- Infected (peri)pancreatic necrosis is defined as one of the following (in the order from the least to the most invasive):
  - gas bubbles within (peri)pancreatic necrosis on CT, or
  - a positive culture of (peri)pancreatic necrosis obtained by image-guided FNA, or
  - a positive culture of (peri)pancreatic necrosis obtained during drainage and/or necrosectomy.
Discussion

There is agreement in the literature that the important local determinants of severity are the presence of necrosis and the infection status of the pancreatic necrosis.\textsuperscript{94,99,133,137,165,168,187–189} The global survey (presented in Chapter 5) indicated that there was little agreement as to the extent of hypoperfusion required to diagnose necrosis. More than a third (35\%) of the survey respondents considered that the diagnosis of necrosis on initial (early) CT required detection of any hypoperfusion, and 31\% considered it needed hypoperfusion of more than 30\% of the pancreas. Given a lack of convincing evidence in the literature, the recommendation is that the diagnosis of necrosis requires detection of any area of hypoperfusion on initial (early) CT. Whether it is necessary to repeat the imaging to define more accurately the extent of necrosis (< 30 \% and > 30\%) will require further evidence (discussed in more detail in the concluding chapter of this thesis).

Peripancreatic and pancreatic necrosis that do not contain necrosis were not considered to be relevant to the classification of severity by 80\% of the survey respondents. It was generally accepted that both peripancreatic and pancreatic lesions are important determinants of severity, and that it is sometimes difficult to distinguish between them.\textsuperscript{100,101,103,190,191} The survey (presented in Chapter 5) indicated that there was no agreement about whether pancreatic lesions were more important than peripancreatic lesions as determinants of severity (49\%) or were not more important (43\%). Furthermore, although some patients do develop pancreatic necrosis alone or peripancreatic necrosis alone, the overwhelming majority of patients with necrotising pancreatitis develop both of them together. For these reasons, no distinction is made between them in the classification of severity, but this is an area that may need to be
modified with new evidence (discussed in more detail in the concluding chapter of this thesis).

Pancreatic infection can be diagnosed both non-invasively and invasively. Procalcitonin is a promising serological marker of pancreatic infection, and especially pancreatic infection in conjunction with OF.\textsuperscript{157} However, its reported pooled specificity in meta-analyses is 83\%–91\%, and it cannot be used as an accurate sole diagnostic test for pancreatic infection.\textsuperscript{192,193} It is likely that combination of procalcitonin with other markers of infection (clinical, biochemical, radiological) would increase the accuracy, but this is an area that requires further evidence.

6.2.2 Systemic determinant

The systemic determinant of severity is OF due to AP.

\textbf{Definitions}

- Organ failure is defined for each system on the basis of the SOFA score\textsuperscript{194} (Table 6.1), i.e., a score $\geq 2$ in the assessed organ system or using a defined threshold, as shown here:
  - Respiratory: $\text{PaO}_2/\text{FiO}_2 \leq 300$
  - Renal: creatinine $\geq 171$ μmol/L ($\geq 2.0$ mg/dL)
  - Cardiovascular: use of sympathomimetic drugs (any dose)
  - Persistent OF is evidence of OF in one or more organ systems during at least 48 hours.
• Transient OF is evidence of OF in one or more organ systems during less than 48 hours.

Table 6.1 SOFA score

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>&gt; 400</td>
<td>&lt; 400</td>
<td>&lt; 300</td>
<td>&lt; 200</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>&gt; 70</td>
<td>0–70</td>
<td>Dopamine ≤ 5.0 or dobutamine (any dose)</td>
<td>Dopamine 5–14.9 or epi ≤ 0.1 or norepi ≤ 0.1</td>
<td>Dopamine ≥ 15 or epi &gt; 0.1 or norepi &gt; 0.1</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>creatinine, µmol/L</td>
<td>&lt; 110</td>
<td>110–170</td>
<td>171–299</td>
<td>300–440</td>
<td>&gt; 440 or dialysis</td>
</tr>
<tr>
<td>mg/dL</td>
<td>&lt; 1.2</td>
<td>1.2–1.9</td>
<td>2.0–3.4</td>
<td>3.5–4.9</td>
<td>&gt; 5.0 or dialysis</td>
</tr>
</tbody>
</table>

Abbreviations: epi, epinephrine; MAP, mean arterial pressure; norepi, norepinephrine; SOFA, Sepsis-related Organ Failure Assessment.

Discussion

Several different aspects of OF were considered for inclusion in the new classification of severity. One of them was the timing of OF. There is evidence from three single-
centre studies demonstrating that “early” OF is associated with a higher mortality, but limitations in each of these studies might confound the observed difference in mortality between the “early” and “late” groups. Early necrosectomy was advocated in two early studies, but has now been abandoned because of an extremely high mortality. The definitions used for “organ failure” also have room for revision because they included SIRS, sepsis, and pancreatic bed bleeding. In one study, a referral bias might have influenced the results. Furthermore, several other studies showed that duration/reversibility of OF, irrespective of the time of onset of OF, is the most important aspect of OF. The latter notion was supported by recent guidelines. Given the lack of accord, the issue of the timing of OF will require further consideration and probably further prospective evaluation from non-intervention studies involving secondary and tertiary centres.

The importance of the duration of OF was also considered. The survey results (presented in Chapter 5) showed that 53% of the respondents would require evidence of OF in one or more organ systems during two consecutive 24-hour periods for the diagnosis of persistent OF, although 33% considered that three consecutive 24-hour periods should be required. Another consideration was about which organs are the most important to consider when diagnosing OF, and there was agreement from the meeting and the survey, in line with the literature, that three organ systems should be considered (respiratory, renal and cardiovascular). The survey also revealed a difference of opinion with respect to the method used to diagnose OF, with 45% of the respondents opting to diagnose each OF separately using a threshold, rather than a composite score with a number of levels (55%). Because of this difference and lack of
convincing evidence in the literature, both alternatives for the diagnosis of OF were included in the definitions.

6.3 Classification of severity

The definitions used for the categories of severity are based on attributes of the local determinants (absent, sterile, or infected [peri]pancreatic necrosis) and the systemic determinants (absent, transient, or persistent OF) as well as the possibility of their interaction.

Definitions

• Mild AP is characterised by the absence of both (peri)pancreatic necrosis and OF
• Moderate AP is characterised by the presence of either sterile (peri)pancreatic necrosis or transient OF
• Severe AP is characterised by the presence of either infected (peri)pancreatic necrosis or persistent OF
• Critical AP is characterised by the presence of infected (peri)pancreatic necrosis and persistent OF.

Discussion

There are two main principles upon which the new classification of severity is founded. First, it is based on actual factors of severity rather than factors that are predictive of severity. The use of multifactorial scoring systems (e.g., APACHE II score, Ranson criteria) to predict severity was incorporated into the Atlanta
classification and, undoubtedly, was an important development 20–30 years ago when imaging was not sophisticated and the importance of OF in AP was not fully recognised. However, these scoring systems are all plagued by a significant misclassification error which limits their utility in clinical practice and in recruitment of individual patients into clinical trials. Notwithstanding the above, the prediction of severity is still a valuable concept but, in order to improve performance it should predict the actual factors of severity, i.e., pancreatic necrosis and OF. A recent example of this is the measurement of angiopoietin-2, a marker of vascular leak syndrome, in predicting persistent OF. Identification of early markers of persistent OF is important because there is a concern, especially among intensivists, that patients are often admitted to ICU too late.

Second, the new classification defines severity solely on the basis of factors that have a causal association with severity. In AP, these factors are pancreatic necrosis and OF. The literature is replete with studies that demonstrate a statistically significant association between other factors and the severity of AP. While possibly statistically correct, it is worth noting that these associations are non-causal, with a confounding and effect-cause relationship being most common. As such, these associations are meaningless and may even be misleading in classifying severity.

When the above principles were applied, four categories of severity resulted. While there was strong support (by 88% respondents) for this four-category classification in the global survey, and it was considered to be useful for both clinical practice (90%) and research (91%), it might be questioned as to what particular advantage it has over two categories. Ultimately, the answer to this will be determined as the new
classification is applied to the care of patients, to plotting of the clinical course, and to audit of clinical experience. For now, an obvious clinical advantage is that the definitions are easy-to-use, standardised, and unambiguous and, as such, will be an aid to monitoring the disease course and in communication between clinicians. In the context of clinical research, the four-category classification of severity will also prove useful in selecting more homogeneous patients for clinical trials and evaluating the effect of treatment (e.g., upstaging the severity as an endpoint of intervention studies).

The classification of AP severity continues to evolve. Further modifications will be required in the future, driven by systematic review of new data. However, at this time there is sufficient evidence, expert opinion, and justification to apply this determinant-based classification of AP severity in both clinical practice and research.
SUMMARY OF PART I

The use of two categories to classify the severity of AP has been in wide use but has not been based on rigorous evidence. The classification systems used so far have been rather crude in selecting patients for clinical trials, and have also had a limited potential to capture the beneficial effect of a certain treatment on severity of disease. In Chapter 3, an evidence-based foundation for classifying the severity of AP was presented. In its support, it is argued that the classification of severity should be based on the actual determinants of severity rather than descriptors of severity. The literature amply demonstrates that both local and systemic determinants are important. Local determinants relate to whether there is a local complication or not, and if present, whether it is sterile or infected. Systemic determinants relate to whether there is OF or not, and if present, whether it is transient or persistent. The derivation of a classification based on the available evidence for the determinants of severity results in more categories of severity than the traditional binary approach used to date.

Chapter 4 investigated whether there is an interaction between determinants of severity. The outcomes of 1478 patients were statistically aggregated and it was found that the risk of death was two times higher in patients with both determinants in comparison with patients with one determinant only. This demonstrated that the presence of a determinant can modify the effect of another, such that the presence of both IPN and persistent OF has a greater effect on severity than either alone. In statistical terms, this phenomenon is called “interaction” and provides a rationale for four categories of severity in AP.
The concept of a new classification of severity was the subject of a global survey of pancreatologists, and was presented in Chapter 5. A total of 240 pancreatologists from 49 countries participated in the survey. There was very strong support for a classification of severity of AP that included four categories (“mild”, “moderate”, “severe”, and “critical”) by 88% respondents. In contrast, only 19% respondents considered that a binary approach to classification is adequate for modern day clinical practice and research. The survey also benchmarked opinions of leading pancreatologists with regard to definitions of local and systemic determinants of severity in AP.

The concluding chapter of Part I (Chapter 6) presented the new determinant-based classification of severity. The distinct features of this classification are that it is based on actual factors of severity rather than factors that are predictive of severity and that it defines severity solely on the basis of factors that have a causal association with severity. Chapter 6 also provided a set of concise up-to-date definitions of all the entities pertinent to classifying the severity of AP. This ensures that the determinant-based classification of severity can be used in a uniform manner.
PART II

OPTIMISATION OF ENTERAL NUTRITION IN ACUTE PANCREATITIS

The literature review in Chapter 1 has demonstrated that nasojejunal feeding with an elemental formulation is considered the current best standard of care in patients with predicted severe AP. This practice is consistent with the recent major paradigm shift in the nutritional management of critically ill patients in a wide range of diseases. However, there remain a number of unanswered questions, and more studies are needed to determine optimal enteral nutrition management specifically for patients with AP. In particular, it is not known whether enteral tube feeding is best delivered into the jejunum, whether an elemental formulation is optimal, and whether there may be an advantage in administering enteral tube feeding to patients other than those with a predicted severe course of the disease.

Part II (Chapters 7–10) focuses on the above three aspects. Chapter 7 evaluates the safety, tolerance, and efficacy of nasogastric tube feeding and compares it with nasojejunal tube feeding. Chapter 8 presents the rationale for administering nasogastric tube feeding to patients with non-severe AP. Chapter 9 describes the results of RCT of early nasogastric tube feeding versus NBM in patients with mild to moderate AP. Chapter 10 evaluates the tolerance and efficacy of different enteral nutrition formulations in AP.
Chapter 7

SAFETY, TOLERANCE, AND EFFICACY OF NASOGASTRIC TUBE FEEDING IN ACUTE PANCREATITIS

7.1 Introduction

Enteral nutrition is preferred to parenteral nutrition because it leads to significantly better glycemic control, decreases infectious complications, reduces the need for surgery, and reduces mortality. With these benefits apparent, one of the unanswered questions has been to determine if there is an optimal site for tube placement during feeding administration. The alternatives include post-pyloric (mainly, nasojejunal) and pre-pyloric (nasogastric) tube placement. The former usually requires the assistance of an endoscopist or a radiologist, and this may result in a delay in commencing enteral nutrition. This delay may have an impact on the clinical outcome because it is now believed that enteral nutrition should commence as soon as possible after adequate fluid resuscitation in order to maximise clinical benefit. In contrast, a nasogastric feeding tube can usually be inserted immediately and with ease, such that pre-pyloric feeding can be started without delay.

A number of RCTs and the latest meta-analysis have demonstrated the equivalence of nasogastric and nasojejunal tube feeding in terms of safety and tolerance in critically ill patients. While this may be true for this group of patients, it is recognised that
patients with AP are particularly prone to gastric ileus because of the subjacent inflamed pancreas.\textsuperscript{206} This has been given as a reason for preferentially providing enteral nutrition into the jejunum. Another reason given is to avoid the provision of enteral nutrition proximal to the jejunum where there is concern that it might induce exocrine pancreatic stimulation and consequently a risk of increased severity of AP.\textsuperscript{100,168} Most studies in patients with AP have employed nasojejunal tube feeding, but there are some studies that employed nasogastric tube feeding.

The only review on nasogastric feeding in AP available in the literature attempted to define the feasibility of this route of nutrition by meta-analyzing the data from RCTs of nasogastric versus “conventional” nutrition.\textsuperscript{207} The pooled estimates and variance of the treatment effect were based on the statistical aggregation of the results from studies with essentially different comparators, i.e., total parenteral feeding and nasojejunal tube feeding. Such an approach might be misleading because parenteral feeding is no longer considered the first-line approach in AP. Moreover, there was a marked heterogeneity in baseline risk among the studies included in that meta-analysis, particularly in regards to age and gender ratio\textsuperscript{75,208}, and incorrect pooled estimates were presented due to inaccurate data input\textsuperscript{208,209}. Furthermore, the previous review did not determine the safety, tolerance, and efficacy of nasogastric tube feeding alone.

### 7.2 Study aim

The aim of this study was to determine the safety and tolerance of nasogastric tube feeding alone and to assess the relative efficacy of nasogastric versus nasojejunal
feeding in patients with AP. This was done by analyzing all of the literature (randomised and non-randomised studies) relating to AP and use of nasogastric tube feeding.

7.3 Methods

7.3.1 Search strategy

A computerised literature search of the Cochrane Central Register of Controlled Trials, EMBASE, and MEDLINE until June 30, 2011 was conducted. The search strategy for the Cochrane Central Register of Controlled Trials was “acute pancreatitis” and “nutrition”. The search strategy for EMBASE included the terms “acute pancreatitis” and “enteral nutrition” or “enteral feeding”. The search strategy for MEDLINE was “acute pancreatitis” (Title/Abstract) and “enteral nutrition” (Title/Abstract) or “enteral feeding” (Title/Abstract). No language restrictions were applied. From the studies on enteral nutrition in AP, only data on patients receiving enteral feeding formula via nasogastric tube were extracted. Bibliographies of all selected articles that included information on nasogastric tube feeding in AP were reviewed for other relevant articles.

7.3.2 Selection criteria

The following selection criteria were used to identify published studies for inclusion in this systematic review:

- study design – cohort study or RCT
- population – patients with AP
- intervention – nasogastric tube feeding
- outcome – at least one of the following outcomes: tolerance, OF, infectious complications, and mortality.

7.3.3 Quality assessment

The methodological quality of the included RCTs was estimated using a previously published quality score. It consists of eight parameters (randomisation, analysis, blinding, patient selection, comparability of groups at baseline, extent of follow-up, treatment protocol, co-interventions, and outcomes) with a quality score range from 0 to 16 points.

7.3.4 Statistical analysis

Chosen a priori, a meta-analysis (Review Manager, Version 5.0 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) was performed on the data from the RCTs of nasogastric versus nasojejunal feeding. The outcome data were combined to determine the RR with its 95% CI. The presence of heterogeneity was assessed using the $I^2$ measure, with $I^2 > 20\%$ indicating significant heterogeneity. Irrespective of the degree of heterogeneity of effect among the included trials, a random-effects model was used.
7.4 Results

7.4.1 Patient characteristics

A total of 397 publications were identified using the above search strategy. Of these, 392 articles did not meet the inclusion criteria and were subsequently excluded. Figure 7.1 details the selection process. A total of five studies were included in this systematic review.75,208,209,211,212

One study was a cohort study211, whereas four other studies were RCTs75,208,209,212. The control groups for the RCTs were nasojejunal feeding in three and parenteral feeding in the fourth. Table 7.1 demonstrates the characteristics of studies included in this review, including the assessment of study quality. All the studies were conducted in patients with predicted severe AP (as defined by the authors). Overall, 131 patients who received nasogastric tube feeding were identified from these studies. The severity of the patients at admission was comparable in all five cohorts, based on APACHE II scoring. Table 7.2 presents the baseline characteristics of patients who received nasogastric tube feeding.
Figure 7.1 Selection of eligible studies

Potentially relevant studies identified (n = 397)

Studies excluded: n = 254 – not clinical studies on enteral nutrition in acute pancreatitis

Potentially appropriate studies to be included in the systematic review (n = 143)

Studies excluded: n = 138 – not studies on nasogastric feeding in acute pancreatitis

Studies included in systematic review (n = 5)
Table 7.1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Design</th>
<th>Control group</th>
<th>APACHE II score</th>
<th>Feeding start</th>
<th>Feeding formulation</th>
<th>Duration of nutrition</th>
<th>Quality of studies$^8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eatock et al, 2000$^{211}$</td>
<td>UK</td>
<td>Cohort</td>
<td>N/A</td>
<td>10 (4–28)$^6$</td>
<td>&lt; 48 hours of admission</td>
<td>Semi-elemental</td>
<td>Not stated</td>
<td>N/A</td>
</tr>
<tr>
<td>Eatock et al, 2005$^{209}$</td>
<td>UK</td>
<td>RCT</td>
<td>Nasojejunal</td>
<td>10 (7–18)$^6$</td>
<td>72 (24–72) hours after onset</td>
<td>Semi-elemental</td>
<td>5 days</td>
<td>14</td>
</tr>
<tr>
<td>Kumar et al, 2006$^{208}$</td>
<td>India</td>
<td>RCT</td>
<td>Nasojejunal</td>
<td>10.5 ± 3.8$^1$</td>
<td>48–72 hours of admission</td>
<td>Semi-elemental</td>
<td>7 days</td>
<td>13</td>
</tr>
<tr>
<td>Eckerwall et al, 2006$^{75}$</td>
<td>Sweden</td>
<td>RCT</td>
<td>Parenteral</td>
<td>10 (8–13)$^6$</td>
<td>&lt; 24 hours of admission</td>
<td>Polymeric</td>
<td>6 (5–9)$^9$ days</td>
<td>14</td>
</tr>
<tr>
<td>Singh et al, 2011$^{212}$</td>
<td>India</td>
<td>RCT</td>
<td>Nasojejunal</td>
<td>8.5 (2–19)$^6$</td>
<td>10 (4–23)$^6$ days after onset</td>
<td>Semi-elemental</td>
<td>7 days</td>
<td>13</td>
</tr>
</tbody>
</table>

Footnote: $^8$Range of quality score is 0 to16; $^6$values are median (range); $^1$values are mean ± standard deviation. Abbreviations: APACHE, Acute physiology and chronic health evaluation; RCT, randomised controlled trial; N/A, not available.
Table 7.2 Characteristics of patients receiving nasogastric tube feeding

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Male:female</th>
<th>Aetiology</th>
<th>Biliary</th>
<th>Alcohol</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eatock et al, 2000\textsuperscript{11}</td>
<td>47 (27–96)\textsuperscript{a}</td>
<td>12:14</td>
<td>18</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Eatock et al, 2005\textsuperscript{209}</td>
<td>63 (47–74)\textsuperscript{a}</td>
<td>14:13</td>
<td>16</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Kumar et al, 2006\textsuperscript{208}</td>
<td>43.3 ± 12.8\textsuperscript{b}</td>
<td>14:2</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Eckerwall et al, 2006\textsuperscript{75}</td>
<td>71 (58–80)\textsuperscript{b}</td>
<td>10:14\textsuperscript{c}</td>
<td>14\textsuperscript{f}</td>
<td>3\textsuperscript{f}</td>
<td>7\textsuperscript{f}</td>
<td></td>
</tr>
<tr>
<td>Singh et al, 2011\textsuperscript{212}</td>
<td>39.1 ± 16.7\textsuperscript{d}</td>
<td>28:11</td>
<td>12</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: \textsuperscript{a}Before exclusion of protocol violator (one patient); \textsuperscript{b}values are median (range); \textsuperscript{c}values are mean ± standard deviation.

7.4.2 Safety and tolerance of nasogastric tube feeding

Nasogastric feeding-related outcomes, including safety and tolerance, are presented in Table 7.3. Full tolerance was achieved in 107 of 131 (82%) patients who did not require temporary reduction, stoppage, or withdrawal of nasogastric feeding. The 24 patients who had a modification of the nasogastric tube feeding regimen presented signs of gastric ileus (n = 7), troublesome diarrhoea (n = 14), or repeatedly removed their feeding tube (n = 3).
Table 7.3 Tolerance of nasogastric tube feeding in the included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total patients</th>
<th>Troublesome diarrhoea n, (%)</th>
<th>Tube removal n, (%)</th>
<th>Gastric retention n, (%)</th>
<th>Exacerbation of pain following feeding, n, (%)</th>
<th>Achievement of nutritional goal</th>
<th>Full tolerance of feeding n, (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eatock et al, 2000211</td>
<td>26</td>
<td>3 (11.5)</td>
<td>1 (3.8)</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
<td>Not stated</td>
<td>19 (73.1)</td>
</tr>
<tr>
<td>Eatock et al, 2005209</td>
<td>27</td>
<td>3 (11.1)</td>
<td>1 (3.7)</td>
<td>0 (0)</td>
<td>2 (7.4)</td>
<td>21 patients (78%) after 60 hours</td>
<td>23 (85.1)</td>
</tr>
<tr>
<td>Kumar et al, 2006208</td>
<td>16</td>
<td>4 (25)</td>
<td>1 (6.3)</td>
<td>0 (0)</td>
<td>1 (6.3)</td>
<td>16 patients (100%) by day 7*</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td>Eckerwall et al, 200625</td>
<td>23</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (13)</td>
<td>Not stated</td>
<td>15 patients (66%) by day 7</td>
<td>20 (86.9)</td>
</tr>
<tr>
<td>Singh et al, 2011212</td>
<td>39</td>
<td>4 (10.4)</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
<td>3 (7.7.)</td>
<td>Not stated</td>
<td>34 (85.6)</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>14 (10.7)</td>
<td>3 (2.3)</td>
<td>7 (5.3)</td>
<td>6 (4.5)</td>
<td>N/A</td>
<td>107 (82.0)</td>
</tr>
</tbody>
</table>

Footnote: †Did not require temporary reduction, stoppage or withdrawal of feeding; *six patients were supplemented by parenteral nutrition during the commencement of feeding. Abbreviation: N/A, not available.
7.4.3 Other clinical outcomes

The other clinically meaningful outcomes of the studies are summarised in Table 7.4. Sixty-one of 92 (45%) patients required ventilatory support. There was no evidence of aspiration pneumonia in any of the patients. Infected pancreatic necrosis was revealed in 15 (12%) of patients. Multiple OF developed in 21 (16%) of patients. The mortality rate was 15%.
Table 7.4 Outcomes of patients who underwent nasogastric feeding in the included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total patients (n)</th>
<th>Patients on ventilatory support n, (%)</th>
<th>Patients with MOF n, (%)</th>
<th>Infected pancreatic necrosis n, (%)</th>
<th>Surgery n, (%)</th>
<th>Mortality n, (%)</th>
<th>LOS, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eatock et al, 2000</td>
<td>26</td>
<td>11 (42.3)</td>
<td>6 (23.1)</td>
<td>5 (19.2)</td>
<td>10 (38.5)</td>
<td>4 (15.4)</td>
<td>17.5 (3–82)</td>
</tr>
<tr>
<td>Eatock et al, 2005</td>
<td>27</td>
<td>7 (25.9)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>5 (18.5)</td>
<td>16 (10–22)</td>
</tr>
<tr>
<td>Kumar et al, 2006</td>
<td>16</td>
<td>15 (93.8)</td>
<td>3 (18.8)</td>
<td>5 (31.3)</td>
<td>1 (6.3)</td>
<td>5 (31.3)</td>
<td>24 ± 14.3</td>
</tr>
<tr>
<td>Eckerwall et al, 2006</td>
<td>23</td>
<td>2 (8.7)</td>
<td>1 (4.3)</td>
<td>1 (4.3)</td>
<td>1 (4.3)</td>
<td>1 (4.3)</td>
<td>9 (7–14)</td>
</tr>
<tr>
<td>Singh et al, 2011</td>
<td>39</td>
<td>26 (66.7)</td>
<td>11 (28.2)</td>
<td>4 (10.2)</td>
<td>4 (10.2)</td>
<td>4 (10.2)</td>
<td>17 (1–73)</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>61 (46.5)</td>
<td>21 (16.0)</td>
<td>15 (11.5)</td>
<td>16 (12.2)</td>
<td>19 (14.5)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Abbreviations:** MOF, multiple organ failure; LOS, length of hospital stay; NA, not available.
7.4.4 Meta-analysis

The meta-analysis was restricted to randomised studies of nasogastric versus nasojejunal feeding. In three eligible trials, a total of 82 patients received enteral nutrition via the nasogastric route and 75 patients via the nasojejunal route.\textsuperscript{208,209,212}

The use of nasogastric feeding resulted in a non-significant reduction in the risk of death (RR 0.71; 95% CI 0.38 to 1.32; \(p = 0.28\), Figure 7.2). The number of nutrition-associated adverse events was similar between the two groups. As a consequence, nasogastric feeding was associated with a non-significant increase in the risk of troublesome diarrhoea (RR 1.39; 95% CI 0.57–3.36; \(p = 0.47\), Figure 7.3) and a non-significant decrease in the risk of pain relapse following feeding (RR 0.84; 95% CI 0.27–2.59; \(p = 0.76\), Figure 7.4). Overall, patients in both groups did not differ significantly in terms of intolerance to feeding (RR 1.23; 95% CI 0.59–2.55; \(p = 0.57\)) (Figure 7.5). There was no heterogeneity between the study results for all comparisons (\(I^2 = 0\%\)).

\textbf{Figure 7.2} Random effects model of the risk ratio of death associated with nasogastric feeding in comparison with nasojejunal feeding
Figure 7.3 Random effects model of the risk ratio of diarrhoea associated with nasogastric feeding in comparison with nasojejunal feeding

Figure 7.4 Random effects model of the risk ratio of pain exacerbation associated with nasogastric feeding in comparison with nasojejunal feeding

Figure 7.5 Random effects model of the risk ratio of intolerance of feeding associated with nasogastric feeding in comparison with nasojejunal feeding
7.5 Discussion

This systematic review has demonstrated the safety and tolerance of nasogastric tube feeding in at least four out of five patients with AP. The study population was limited to patients with a predicted severe course of AP and the clinical outcomes were within the expected range for this category of patients. Nasogastric tube feeding-related problems occurred in less than 20% of patients and they were relatively minor. There were no recorded cases of aspiration pneumonia.

Three RCTs included in the meta-analysis consistently yielded no tangible difference between nasogastric and nasojejunal feeding in terms of safety and tolerance.\textsuperscript{208,209,212} It should be acknowledged that the trials had some flaws. In particular, it was argued that it is likely that jejunal feeding in the trial from Glasgow\textsuperscript{209} was actually duodenal (because true jejunal placement would have been difficult with the types of feeding tubes and placement techniques used), meaning that both feeding arms may have caused equivalent stimulation of pancreatic secretion\textsuperscript{213}. The shortcoming of the RCT by Kumar and colleagues\textsuperscript{208} was that there was a considerable delay (7.8 ± 6.5 and 5.7 ± 4.7 days after symptom onset in the nasogastric and nasojejunal groups, respectively) and that enteral nutrition was commenced late. In addition, the authors observed a high mortality (31% and 29% in the nasogastric and nasojejunal groups, respectively) which might reflect the tendency towards conservative management of patients with IPN. The trial by Singh and colleagues\textsuperscript{212} suffered from the same shortcoming, i.e., the feeding protocol in both groups was commenced relatively late (10 [4–23] and 11 [3–48] days after symptom onset in the nasogastric and nasojejunal groups, respectively). Apart from these concerns, the three RCTs were insufficiently
powered individually to detect any difference or to demonstrate equivalence between
the studied groups in terms of mortality. An adequately powered RCT would need to
enrol nearly 200 patients per arm in order to show a decrease in mortality from 14%
(average rate in the nasogastric group in the present review) to 6% (best results in the
nasojejunal group of RCTs on enteral versus parenteral nutrition\textsuperscript{168,201}) with 80%
power and $\alpha = 0.05$ (two-sided). Such a sample size is appreciably large, even for a
multicentre study.

Another relevant issue in considering nasogastric tube feeding is the effect on exocrine
pancreatic function. It was shown by O’Keefe and colleagues that all forms of enteral
nutrition stimulate pancreatic secretion.\textsuperscript{214} In particular, when compared with placebo
saline, an oral liquid polymeric diet resulted in a significantly higher level of amylase
($p < 0.01$) and lipase ($p < 0.01$); a duodenal polymeric enteral formula led to increased
levels of amylase ($p < 0.01$), lipase ($p < 0.01$), and trypsin ($p < 0.01$); and a duodenal
elemental feeding formula resulted in an elevated level of lipase ($p < 0.05$). The same
research group also compared the pancreatic secretory response to tube feeding
delivered into the duodenum and the mid (40–60 cm distal to the ligament of Trietz)
and distal (100–120 cm distal to the ligament of Trietz) jejunum.\textsuperscript{121} Even though the
authors did not find a direct relationship between the decrease in enzyme secretion and
distance down the mid-distal jejunum, they demonstrated significantly lower secretion
of trypsin ($p < 0.01$) and lipase ($p < 0.05$) in response to the elemental formula
delivered into the jejunum (40 cm or more distal to the ligament of Trietz) in
comparison with the duodenum. Moreover, the trypsin and lipase secretory response in
the mid-distal jejunum group was as low as in the control group (fasting).
However, it should be noted that these studies of the effects of enteral feeding on exocrine pancreatic function were in healthy subjects.\textsuperscript{121,214} There is now convincing evidence that patients with AP have significantly lower rates of enzyme secretion compared with healthy subjects.\textsuperscript{215} Furthermore, when patients with mild to moderate AP were compared with those with severe AP, a lower secretion of trypsin (6-fold), amylase (22-fold), and lipase (42-fold) was found in the latter group, suggesting that pancreatic enzyme secretion is inversely related to the severity of AP. In line with this finding, another study showed an 86\% rate of pancreatic exocrine insufficiency (measured by faecal pancreatic elastase-1) in patients recovering from severe attacks of AP.\textsuperscript{216} Moreover, the severity of pancreatic exocrine insufficiency correlated with the extent of pancreatic necrosis. These data suggest that injured acinar cells are not able to respond fully to the physiological stimuli of secretion which may go some way towards explaining the findings of this study that, contrary to popular belief, nasogastric tube feeding does not appear to aggravate the severity of AP.

7.6 Conclusion

The present systematic review has appraised the current evidence regarding the use of nasogastric tube feeding in patients with AP. The evidence base is relatively small (and limited to patients with predicted severe AP), but does show that enteral nutrition given via the nasogastric route is safe and well tolerated in the majority of patients. It also suggests that nasogastric tube feeding might be best tolerated if started as early as possible, and because of the ease of insertion, it could be started within 24 hours of hospital admission.
Chapter 8

RANDOMISED TRIAL OF EARLY NASOGASTRIC TUBE FEEDING VERSUS NIL-BY-MOUTH IN MILD TO MODERATE ACUTE PANCREATITIS – RATIONALE AND METHODOLOGY

The previous chapter demonstrated that all the published studies on the use of nasogastric tube feeding were conducted in patients with predicted severe AP. At the same time, there are no published clinical studies, let alone randomised trials, that have assessed the safety, tolerance, and efficacy of nasogastric tube feeding in patients other than those with predicted severe AP. This chapter provides a rationale for early use of nasogastric tube feeding in patients with a non-severe course of disease. It also describes the methodology of the randomised Early nasogastric tube Feeding versus NBM regimen in patients with mild to moderate Acute Pancreatitis (EFAP) trial.

8.1 Introduction

Enteral tube feeding in patients with predicted severe AP has proven to be an important part of their management. By contrast, it is traditionally believed that patients with non-severe AP should be kept on a NBM regimen, because early commencement of oral refeeding may exacerbate pain. Oral intake of food is usually initiated when abdominal pain has subsided, parenteral narcotics are no longer required, abdominal tenderness has markedly decreased, nausea and vomiting have ceased, and/or bowel sounds are present. Further, the current European Society for
Clinical Nutrition and Metabolism guidelines state that in non-severe AP “oral food intake should be tried as soon as possible”. However, this practice often leads to occurrence of pain relapse and prolonged hospitalisation.

The pathophysiology of pain relapse in AP is unclear. Because patients with pain relapse tend to have a longer duration of initial abdominal pain, persistent elevation of serum enzymes, and higher Balthazar’s scores on admission, it may well be that patients with pain relapse are those with more severe AP. However, due to the significantly longer post-refeeding length of hospital stay and the absence of difference in the severity scores between patients with and without pain relapse, premature oral refeeding could also be responsible for the pain relapse.

In an attempt to prevent pain relapse in AP after oral refeeding, a French research group suggested the use of a long-acting somatostatin analogue. In their study, only one of 23 (4.3%) patients treated with one intramuscular injection of lanreotide 30 mg on the day before refeeding had a recurrence of pain from AP, but 15 (65.2%) patients also experienced at least one adverse effect from the drug. Because this was an uncontrolled pilot study, a multicentre, randomised, placebo-controlled, double-blind trial was subsequently undertaken. Unfortunately, it was found that the injection of lanreotide 30 mg 24 hours prior to oral refeeding had no influence on either the rate of pain relapse within the week following oral refeeding or the length of hospital stay.
8.2 Hypothesis

The hypothesis of this study is that early (within 24 hours of hospital admission) administration of nasogastric tube feeding prevents pain relapse after oral refeeding and shortens length of hospital stay in patients with mild to moderate AP.

8.3 Rationale

There is one small study (n = 28) in the literature that was specifically designed to assess the role of enteral tube feeding in preventing the risk of pain relapse in patients with AP, irrespective of the severity of AP.222 A RCT from India compared oral bolus refeeding (started on 5 [5–18] days after onset of AP) with nasojejunal tube refeeding (started on 7 [6–17] days) and found a lower risk of pain relapse in jejunally-refed patients. Further, a RCT from Scotland209 provided indirect evidence of a favourable effect of enteral tube feeding on pain in patients with predicted severe AP by demonstrating no difference in pain and analgesic requirement between early nasogastric and nasojejunal tube feeding administered within 72 hours after onset of pain. Notably, it showed that pain measured by visual analogue score (VAS) decreased markedly from 7 on the first day to 0 on the third day of nutrition in both groups.

There is also reason to believe that enteral feeding is superior to parenteral feeding (which is not different from a NBM regimen in terms of gut rest) in improving tolerance of oral refeeding in patients with AP. A RCT from the United States226 demonstrated that reintroduction of oral feeding was better tolerated in patients who were allocated to enteral feeding, with 80% (21 of 26) advancing to an oral diet
without problems, in comparison with 63% (17 of 27) in the parenterally-fed group. Further, in the trial from the United Kingdom,73 17 patients with AP were randomised (nine in the enterally-fed group, eight in the parenterally-fed group). Enteral nutrition was initiated within 6 hours of admission and led to no nutrition-associated complications. Bowel function returned to normal more quickly in the enteral nutrition group, as evidenced by passing flatus (1 [0–2] days versus 2 [1–5] days, p = 0.07) and stool (2 [0–3] day versus 3 [2–9] days, p = 0.01), as well as by resumption of full oral intake (2 [0–3] days versus 3 [2–9] days, p = 0.02). Fatigue, estimated by VAS, improved more rapidly in the enteral group than in the parenteral group (significantly different on day 3, p = 0.01). Altogether, these data question the rationale of fasting patients with AP prior to introduction of oral refeeding. Furthermore, they suggest that early enteral tube feeding may offer two possible benefits in patients with non-severe AP, i.e., prevention of progression in severity of AP and improved tolerance of oral refeeding. In turn, this may lead to a decrease in the risk of pain relapse and shorten the length of hospital stay (Figure 8.1).
Figure 8.1 Hypothetical mechanism of beneficial effect of enteral tube feeding in non-severe acute pancreatitis
8.4 Study aim

The aim of this randomised study was to compare the safety, tolerance, and efficacy of early enteral tube feeding versus a NBM regimen in patients with mild to moderate AP.

8.5 Methods

8.5.1 Study design

This was a prospective RCT conducted at Auckland City Hospital (Auckland, New Zealand) between February 2010 and March 2011. The Northern X Human Ethics Committee and the Auckland DHB Research Review Committee approved the study protocol (Appendix 3). The study protocol was also registered at www.ClinicalTrials.gov (NCT01128478).

The inclusion criteria were

- diagnosis of AP
- age > 18 years
- written informed consent.

Diagnosis of AP required at least two of the following three criteria:

- abdominal pain suggestive of AP
- serum amylase and/or pancreatic amylase activity at least three times the upper limit of normal
• characteristic findings of AP on CT.

Patients were excluded if they had:
• symptoms for more than 96 hours
• severe or critical AP
• chronic pancreatitis
• post-ERCP pancreatitis
• intraoperative diagnosis
• pregnancy (as reported by the patient)
• malignancy
• received nutrition before randomisation
• been previously enrolled into the trial.

Severe or critical AP was defined as the presence of OF and/or pancreatic infection at the time of randomisation (as per the new classification of severity presented in Chapter 6). Organ failure was defined in accordance with the SOFA score as a score ≥ 2 for at least one of three organ systems, i.e., respiratory, renal without pre-existing renal disease, and cardiovascular (Table 6.1). Pancreatic infection was defined as one of the following: gas bubbles within a (peri)pancreatic necrosis on CT, or a positive culture of a (peri)pancreatic necrosis obtained by image-guided FNA during the first percutaneous/endoscopic drainage, minimally invasive or open surgery.
8.5.2 Study groups

There were two study groups:

i) Early tube feeding (ETF): The patients in the intervention group were initially NBM but received enteral nutrition that commenced within 24 hours of hospital admission via a 10 Fr 109 cm (43”) enteral feeding nasogastric tube placed into the stomach (CORFLO® - ULTRA, Corpak Medsystems, Wheeling, IL, USA). A commercially available low-fat feed (Peptisorb®, Nutricia Clinical NZ) was used. Enteral nutrition was started at a rate of 25 mL/h and increased stepwise until 100 mL/h was reached over 24–48 hours. It was continued until the decision of the treating medical team to introduce oral food.

ii) Nil-by-mouth (NBM): The patients in the control group were on a NBM regimen until the decision of the surgical team to introduce oral food.

8.5.3 General patient management

All the patients were managed according to the same clinical care pathway (Appendix 4). All clinical decisions were the responsibility of the treating surgical teams. The teams were independent of the principal investigator of the study. In particular, the transition from tube feeding or NBM was their decision alone. In both groups, intravenous fluids and parenteral narcotics were administered at a rate and frequency decided by the independent surgical management team. The treating surgical teams were responsible for charting all the medications, including analgesia, in which case they were supported by a dedicated hospital pain team. The timing of hospital discharge was solely at the discretion of the treating surgical teams.
8.5.4 Endpoints

The primary endpoint was the total length of hospital stay.

The secondary endpoints were

- presence of oral refeeding intolerance
- time from admission until tolerance of oral food
- time from oral refeeding until hospital discharge
- time from admission until minimal or no pain
- opiate requirements
- change in pain intensity
- time from admission until first flatus
- time from admission until first stool
- change in plasma CRP
- change in white cell count (WCC)
- progression of AP severity
- number and type of interventions during hospital stay
- in-hospital mortality
- hospital readmission.

**Definitions**

Oral refeeding intolerance was defined as putting the patient onto a NBM regimen because of pain relapse, nausea, or vomiting after introduction of oral refeeding.\textsuperscript{227}

The main complaints of patients were monitored until discharge by means of a detailed daily patient diary given to each patient (Appendix 5).
Intensity of pain was assessed using the VAS scored at rest. The VAS consisted of a 10 cm line with numbers from 0 to 10 at 1 cm increments, with 0 representing “no pain” and 10 “the worst possible pain”. Patient was considered to have minimal or no pain if VAS was $\leq 2.227$.

Progression of severity was defined as patient’s upstaging (i.e., from “mild” to “moderate” or from “moderate” to “severe” during hospitalisation) according to the new classification of severity presented in Chapter 6.

Hospital interventions recorded in the study were therapeutic ERCP, cholecystectomy, percutaneous drainage, or necrosectomy.

Hospital readmission was defined as readmission due to exacerbation of abdominal pain within 3 months of hospital discharge.

8.5.5 Assignment

Patients were randomly divided into two groups and allocation concealment was by use of sealed numbered envelopes. The computer-generated assignment was balanced with the use of blocks of four and six to mask the assignment.
8.5.6 Power calculation

The median duration of hospitalisation for mild AP at Auckland City Hospital was 6 ± 1.5 days between 1999 and 2001. A sample size of 70 subjects (35 in each group) was calculated to have 80% power (two-sided \( \alpha = 0.05 \)) to detect a one-day difference in total length of hospital stay between the study arms. An interim analysis was planned after recruitment of half of the patients, and it was agreed that the trial would stop if the analysis showed the study was not going to be able to reach statistical significance for the primary endpoint.

8.5.7 Data storage and analysis

All data were stored in a secure encrypted central Internet-based database MACRO (InferMed Limited, London, UK). The statistical analysis was done using SPSS for Windows version 19 (SPSS Inc, Chicago, IL, USA). Non-parametric statistics was used as the most conservative (no assumption regarding the normality of distribution). Comparison of continuous variables between the groups was performed by the Mann-Whitney U test. Nominal variables were compared between the groups using the Pearson’s Chi-square test or Fisher’s Exact test, as appropriate. Comparison of three or more sets of repeated measures was performed using analysis of variance with the Greenhouse-Geisser adjustment to the degrees of freedom of the F-test or by the Wilcoxon signed ranks test where two sets of repeated measures were made. Kaplan-Meier analysis and the log rank (Mantel-Cox) test were employed to compare the studied groups in terms of time to event outcomes. Values were expressed as the median and 95% CI in the time to event analysis and as the median and interquartile.
range (25th to 75th percentile) in all other analyses. P values < 0.05 were accepted as statistically significant. The analysis was done with respect to intention-to-treat principles.
Chapter 9

RANDOMISED TRIAL OF EARLY NASOGASTRIC TUBE FEEDING VERSUS NIL-BY-MOUTH IN MILD TO MODERATE ACUTE PANCREATITIS – RESULTS AND IMPLICATIONS

The previous chapter described the rationale and methodology of the EFAP trial. This chapter presents the results of that trial and discusses their practical implications. The trial was stopped at the time of the interim analysis because it became apparent that it was not possible to reach a statistical significant difference in the primary endpoint with the calculated sample size.

9.1 Results

9.1.1 Patient flow and characteristics

A total of 78 patients with AP were admitted to Auckland City Hospital during the study period. Of these, 33 met at least one of the exclusion criteria and 10 declined to participate (Figure 9.1).
Figure 9.1 Flow chart of patients in the EFAP trial

- Assessed for eligibility (n = 78)
  - Excluded
    - admitted > 96 h (n = 6)
    - diagnosis > 24 h (n = 7)
    - severe acute pancreatitis (n = 5)
    - chronic pancreatitis (n = 4)
    - malignancy (n = 3)
    - nutrition before randomisation (n = 3)
    - other (n = 5)
    - no consent (n = 10)
  - Randomised (n = 35)
    - Allocated to ETF (n = 17)
      - Received ETF (n = 17)
      - Did not receive ETF (n = 0)
        - Lost to follow-up (n = 0)
          - Analysed (n = 17)
    - Allocated to NBM (n = 18)
      - Received NBM (n = 18)
      - Did not receive NBM (n = 0)
        - Lost to follow-up (n = 0)
          - Analysed (n = 18)
Random allocation of included patients resulted in 17 in the intervention group (ETF) and 18 in the control group (NBM). At baseline, the two groups did not have any significant differences in terms of demographic, anthropometric, or laboratory data (Table 9.1).
### Table 9.1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>ETF</th>
<th>NBM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 (34–60)</td>
<td>55 (36–70)</td>
<td>0.25</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>NZ European</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms, h</td>
<td>18 (6–36)</td>
<td>15 (4–39)</td>
<td>0.86</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Biliary</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Co-morbidity class*</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>26 (24–30)</td>
<td>25 (23–28)</td>
<td>0.41</td>
</tr>
<tr>
<td>Amylase, U/L</td>
<td>841 (221–2117)</td>
<td>848 (497–1142)</td>
<td>0.35</td>
</tr>
<tr>
<td>Pancreatic amylase, U/L</td>
<td>826 (158–1390)</td>
<td>811 (406–1112)</td>
<td>0.41</td>
</tr>
<tr>
<td>WCC, 10⁹/L</td>
<td>10 (8–13)</td>
<td>12 (8–16)</td>
<td>0.36</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>44 (6–167)</td>
<td>66 (16–145)</td>
<td>0.34</td>
</tr>
<tr>
<td>SIRS, pts</td>
<td>6</td>
<td>6</td>
<td>0.93</td>
</tr>
<tr>
<td>Glasgow score</td>
<td>1 (0–2)</td>
<td>2 (0–2)</td>
<td>0.15</td>
</tr>
<tr>
<td>BISAP score</td>
<td>0 (0–1)</td>
<td>0 (0–2)</td>
<td>0.13</td>
</tr>
<tr>
<td>SOFA score</td>
<td>0 (0–1)</td>
<td>0 (0–2)</td>
<td>0.88</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>6 (2–9)</td>
<td>6 (3–11)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

**Footnote:** *As defined by the American Society of Anaesthesiologists guidelines. Values are expressed as the median and interquartile range. **Abbreviations:** BMI, body mass index; WCC, white cell count; CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome; BISAP, Bedside Index Severe Acute Pancreatitis; SOFA, Sepsis-related Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.
9.1.2 Study groups

In the ETF group, 15 of the 17 patients received only nasogastric tube feeding before the introduction of oral feeding. There were no complications associated with insertion of the nasogastric tubes. ETF was started at 22 (16–23) hours after hospital admission. The duration of ETF was 48 (31–96) hours. The average volume of enteral feed given to each patient was 2710 (1060–5000) mL. No patient demonstrated any signs of aspiration. One patient without pancreatic necrosis and OF developed an exacerbation of abdominal pain while on nasogastric tube feeding which settled after the tube was advanced radiologically into the jejunum on day 4. One patient with transient OF on admission (resolved by the time of randomisation) and pancreatic necrosis tolerated nasogastric tube feeding well but his tube was advanced radiologically into the jejunum on day 7 when clinical suspicion of pancreatic infection was raised.

In the NBM group, 16 of the 18 patients were maintained on NBM before introduction of oral feeding. Of the other two patients, one was put on nasogastric tube feeding on day 8 after admission because she did not tolerate oral feeding. The patient had no CT evidence of pancreatic necrosis but had transient respiratory failure on admission (resolved by the time of randomisation). The other patient with pancreatic necrosis but without OF was put on total parenteral nutrition on day 4 after admission because of suspicion of mesenteric ischaemia (resolved on follow-up CT). After withdrawal of parenteral nutrition, he did not tolerate oral feeding and was put on nasogastric feeding on day 12.
9.1.3 Clinical course during the 72 hours following randomisation

The VAS pain score decreased significantly during the 72 hours after randomisation in both groups \( (F = 31.153, p < 0.001) \). Further, it decreased to a significantly greater extent in the ETF group when compared with the NBM group \( (F = 3.275, p = 0.036, \text{ Figure 9.2}) \).

![Figure 9.2: Pain level before and during the 72 hours following randomisation in the two groups](image)

**Figure 9.2** Pain level before and during the 72 hours following randomisation in the two groups

**Footnote:** for each category, the box indicates the median and interquartile range (25th to 75th percentile) and whiskers indicate the minimum and maximum values.
The nausea score decreased significantly during the 72 hours after randomisation in both groups (F = 6.228, p = 0.003) but there was no statistically significant difference between the groups (F = 1.286, p = 0.287). The change in severity of bloating during the 72 hours after randomisation was not statistically significant (F = 1.545, p = 0.224) and there was no statistically significant difference between the groups (F = 0.723, p = 0.469, Table 9.2).

Table 9.2 Main symptoms before and during the 72 hours after randomisation

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>24 h after randomisation</th>
<th>48 h after randomisation</th>
<th>72 h after randomisation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBM</td>
<td>7 (5–9)</td>
<td>4 (3–6)</td>
<td>4 (2–7)</td>
<td>3 (1–4)</td>
<td>0.036</td>
</tr>
<tr>
<td>ETF</td>
<td>9 (7–9)</td>
<td>3 (1–7)</td>
<td>2 (1–6)</td>
<td>1 (0–3)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBM</td>
<td>4 (0–7)</td>
<td>0 (0–5)</td>
<td>0 (0–3)</td>
<td>0 (0–3)</td>
<td>0.29</td>
</tr>
<tr>
<td>ETF</td>
<td>5 (2–8)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBM</td>
<td>2 (0–7)</td>
<td>3 (0–5)</td>
<td>3 (0–4)</td>
<td>3 (0–4)</td>
<td>0.47</td>
</tr>
<tr>
<td>ETF</td>
<td>4 (0–7)</td>
<td>2 (0–5)</td>
<td>3.5 (0–6)</td>
<td>3.5 (0–6)</td>
<td></td>
</tr>
</tbody>
</table>

The change in WCC was significant during the 72 hours after randomisation (F = 6.954 p = 0.003) but there was no statistically significant difference between the groups (F = 1.672, p = 0.204). The change in CRP concentration was not significant during the 72 hours after randomisation (F = 2.520, p = 0.134) and there was no statistically significant difference between the groups (F = 0.230, p = 0.704).
9.1.4  Primary endpoint

The total length of hospital stay in the ETF group was 9 (5–12) days as compared with 8.5 (6–13) days in the NBM group (p = 0.91).

9.1.5  Secondary endpoints

i) Oral refeeding intolerance

Oral feeding was introduced 4 (3.5–6.5) days in the ETF group and 4 (3–5.5) days after hospital admission in the NBM group (p = 0.52). Oral feeding intolerance was observed in one of 17 patients in the ETF group and nine of 18 patients in the NBM group (p = 0.004). Oral feeding intolerance included pain relapses that required cessation of oral feeding in one patient in the ETF group and eight patients in the NBM group (p = 0.009) and nausea/vomiting that required cessation of oral feeding in none of the patients in the ETF group and in six patients in the NBM group (p = 0.02). Time from admission until tolerance of oral food was 5 (4–7) days in the ETF group and 7 (5–9) days in the NBM group (p = 0.162) Time from introduction of oral refeeding until hospital discharge was 3 (1–6.5) days in the ETF group and 4 (2–7) days in the NBM group (p = 0.370).

ii) Overall pain and need for opiates

The use of ETF resulted in significantly fewer patients needing opiates between baseline and 72 hours after randomisation and from 24 hours to 48 hours after
randomisation (Table 9.3). In total, one patient in the ETF group and three patients in the NBM group did not require opiates at 24 hours after randomisation (p = 0.316). At 48 hours after randomisation, nine patients in the ETF group and three patients in the NBM group did not require opiates (p = 0.024, Table 9.3).

Table 9.3 Number of patients not needing opiates before and during the 72 hours after randomisation

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>24 h after randomisation</th>
<th>48 h after randomisation</th>
<th>72 h after randomisation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBM</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>0.033*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002#</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.066§</td>
</tr>
<tr>
<td>ETF</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.48</td>
<td>0.32</td>
<td>0.024</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: *Change from baseline to 72 hours after randomisation; #change from 24 hours to 48 hours after randomisation; §change from 24 hours to 72 hours after randomisation.

One patient in the ETF group and five patients in the NBM group required an additional opiate at any time after randomisation (p = 0.086). Time from admission to minimal or no pain was 4 (95% CI 3.1–4.9) days in the ETF group and 6 (95% CI 5.3–6.7) days in the NBM group (log rank test = 5.16, p = 0.023, Figure 9.3).
iii) Other clinical outcomes

Eight patients required a total of nine interventions in the ETF group and nine patients required a total of 10 interventions in the NBM group (p = 0.981). All but one of the 19 overall interventions were therapeutic ERCP and cholecystectomy. Progression of severity occurred in two patients in the ETF group and two patients in the NBM group (p = 0.95). There was no in-hospital mortality. One patient in the ETF group and two in the NBM group required hospital readmission (p = 0.58).

Time until first flatus was 2 (95% CI 1.1–2.9) days in the ETF group as compared with 2 (95% CI 1.3–2.8) days in the NBM group (log rank test = 0.062; p = 0.80). Time
until first stool was 4 (95% CI 1.25–6.75) days in the ETF group as compared with 4 (95% CI 3.14–4.86) days in the NBM group (log rank test = 0.277; \( p = 0.59 \)).

### 9.2 Discussion

To the best of our knowledge, this is the first randomised trial to compare nasogastric tube feeding with a conventional NBM regimen in patients with AP. It demonstrates that early use of nasogastric tube feeding is as safe as a NBM regimen in patients with mild or moderate severity of the disease. Furthermore, commencement of nasogastric tube feeding within 24 hours of hospital admission results in significantly reduced intensity and duration of initial abdominal pain, need for opiates, and risk of oral refeeding intolerance. These findings have important practical and theoretical implications.

From a practical standpoint, the present trial is important because it used criteria of actual severity to enrol patients in the trial. This is in contrast with previous RCTs on the use of enteral nutrition in AP that used a wide array of predictive tools (APACHE II score, and/or Ranson score, and/or CRP, and/or CT severity index) to enrol patients. However, it is widely acknowledged that these tools invariably introduce a 20%–40% misclassification error. Further, no RCT to date has used a single predictive tool, so it is difficult to extrapolate the data from published studies into clinical practice, and thus the exact study population that benefits from enteral nutrition has been largely unknown. The present trial amplifies the recently acknowledged benefits of ETF in patients with predicted severe AP by showing, for the first time, that patients with actual mild or moderate AP also benefit from ETF. Taking these arguments into
account, it is reasonable to suggest that almost all patients with AP may potentially benefit from early ETF.

From a theoretical standpoint, the present trial adds an important perspective to the discussion regarding the “pancreas rest” concept. A cornerstone of this concept is that avoidance or minimisation of the pancreatic enzyme secretory response might prevent exacerbation of the acute inflammatory process in the pancreas.\textsuperscript{100,121} The corollary is that non-stimulatory nutrition had been widely advocated, being total parenteral nutrition 2–3 decades ago and nasojejunal tube feeding in the last decade. That is why all the RCTs in the past studied non-stimulatory regimens only, i.e., either parenteral nutrition versus NBM,\textsuperscript{230–232} parenteral nutrition versus jejunal tube feeding,\textsuperscript{72–74,78,79,226,233–235} or jejunal tube feeding versus NBM\textsuperscript{88} (Figure 9.4).
Figure 9.4 Place of the present study in the literature

Footnotes: NBM, nil-by-mouth; PN, parenteral nutrition; NJ, nasojejunal tube feeding; NG, nasogastric tube feeding; RCT, randomised controlled trial.
The “pancreas rest” concept was challenged by analysis of the data from three RCTs on nasojejunal versus nasogastric feeding in patients with AP (discussed in detail in Chapter 7), which revealed no difference between non-stimulatory and stimulatory regimens in terms of tolerance of feeding, pancreatic complications, and mortality.\(^{208,209,212}\) Further, a recent RCT compared parenteral nutrition, another form of non-stimulatory feeding, with nasogastric feeding and also found no difference between non-stimulatory and stimulatory regimens in terms of the same outcomes.\(^75\)

The present study bridges the important gap in our knowledge by comparing the third non-stimulatory regimen, NBM, with nasogastric tube feeding head-to-head in a RCT (Figure 9.4). It shows that early administration of nasogastric tube feeding is safe and does not exacerbate the course of AP. Furthermore, it appears that the use of nasogastric tube feeding significantly reduces the intensity and duration of initial pain and prevents pain relapse after oral refeeding.

There are two possible explanations for these findings, both of which are a matter of speculation at this time. First, nasogastric tube feeding might have been non-stimulatory in patients with AP, at least when given as reported. There are two earlier observational studies, both in healthy volunteers, which showed that nasogastric tube feeding does not increase the pancreatic secretory response when the rate of continuous infusion is below 1.5 mL/min.\(^{236,237}\) However, in contrast, there is a much larger body of literature suggesting that nasogastric feeding is stimulatory and may exacerbate the course of AP.\(^{100,121,233}\) Second, the concept of “pancreas rest” might have been fallacious, essentially meaning that early nutrition in any form does not stimulate the pancreas or stimulates it to a level that has no clinical ramifications. Although it has become deeply entrenched in the management of AP, it is worth
noting that the “pancreas rest” concept was never proven in RCTs. Further, a recent RCT of early (within 24 hours of hospital admission) oral feeding ad libitum versus NBM showed that oral feeding does not exacerbate the course of AP and even reduces the total length of hospital stay.\textsuperscript{238} However, that trial was inconclusive because it was open-label, the sample size was limited, the study population comprised patients with predicted mild AP provided the duration of abdominal pain was less than 48 hours. Further, there is a wealth of observational data over recent decades that clearly indicates a link between very early (premature) institution of oral feeding and exacerbation of the course of AP.\textsuperscript{221,239,240} Thus, early nasogastric tube feeding and oral feeding ad libitum should now be compared in an adequately powered RCT to give a definitive answer on whether the “pancreas rest” concept is justifiable or not.

\section{9.3 Limitations}

There are a number of possible limitations to this trial, and these need to be acknowledged. First, the study was open-label because blinding was not possible due to the nature of the study groups. Second, the study population was limited to patients with mild to moderate AP. Although a trial with the same design in patients with severe and critical AP might be desirable, fasting of patients in a hypercatabolic state would be in conflict with the most recent guidelines and pose an ethical dilemma.\textsuperscript{100,168} At the same time, it is pertinent to note that the median APACHE II score in both groups of the trial was 6. In the past, AP patients with an APACHE II score of at least 6 were labelled as having “predicted severe AP” in some RCTs. Third, no difference in terms of the primary endpoint (total length of hospital stay) was demonstrated. This might be due to the policy in our institution for patients with biliary pancreatitis to stay
in hospital for a cholecystectomy. There might also be a number of reasons other than clinical ones that affected length of stay, particularly for older patients. \textsuperscript{241–243} However, it is worth noting that time from admission until tolerance of oral food and time from introduction of oral food until hospital discharge were reduced by 2 days and one day, respectively. Both were deemed to be clinically meaningful results but did not reach a conventional level of statistical significance, likely due to a limited sample size.

\subsection{Conclusion}

Nasogastric tube feeding commenced within 24 hours of hospital admission is safe and well tolerated in patients with mild to moderate AP. Further, when compared with the NBM regimen, it significantly reduces the intensity and duration of initial abdominal pain, need for opiates, and risk of oral refeeding intolerance. Neither nasogastric tube feeding nor the NBM regimen appears to influence the severity of disease, number of interventions, or total length of hospital stay in this trial.
Chapter 10

OPTIMAL ENTERAL NUTRITION FORMULATION IN ACUTE PANCREATITIS

The previous three chapters challenged the notion of putting the pancreas at rest by showing that tube feeding into the stomach is safe and well tolerated in the vast majority of patients with AP. However, it has been known since the groundbreaking experiments by Ivan Pavlov and his disciples that not only the site of feeding but also the composition of enteral feed may affect the pancreatic secretory response and, thus, the question of the optimal enteral nutrition formulation is important, both in the management of patients with AP and for the validity of the “pancreas rest” concept. Both the EFAP trial (Chapters 8 and 9) and the other RCTs of nasogastric tube feeding (Chapter 7) invariably employed an elemental formulation on the basis that it is deemed to be the least stimulatory feed. This chapter explores the safety, tolerance, and efficacy of other enteral nutrition formulations, including polymeric formulations, immunonutrition, probiotics, and fibre-enriched formulations.

10.1 Introduction

The “pancreas rest” concept has been regarded as a key element in the early management of patients with AP. As a consequence, for decades, these patients have received total parenteral nutrition in an attempt to avoid stimulation of pancreatic enzyme secretion. However, over the last decade, a number of RCTs
have consistently shown the superiority of enteral over parenteral nutrition in terms of reducing the rate of infectious complications and death.\textsuperscript{72–74,78,235} Further, a recent meta-analysis of RCTs established the absolute value of enteral nutrition by demonstrating significantly reduced mortality in patients with AP who received enteral nutrition in comparison with those who did not receive any kind of nutrition.\textsuperscript{116}

Now that the benefits of enteral nutrition in patients with AP have become widely accepted, one of the key questions to answer is what is the optimal formulation to use. There are more than 100 different enteral nutrition formulations available.\textsuperscript{244} These can be broadly classified into the following categories:

- Elemental – comprising amino acids or oligopeptides, maltodextrins, and medium-chain and long-chain triglycerides
- Polymeric – comprising non-hydrolyzed proteins, maltodextrins and oligofructosaccharides, as well as long-chain triglycerides
- Immune-enhancing – comprising substrates that have been hypothesised to modulate the activity of the immune system, e.g., immunonutrition (glutamine, arginine, and omega-3 fatty acids), probiotics, fibre-enriched formulation).\textsuperscript{244}

In patients with AP, the use of elemental over polymeric formulations presents a number of theoretical advantages because it is believed that an elemental formulation has superior absorption from the intestine, stimulates pancreatic secretions to a lesser degree, and is better tolerated.\textsuperscript{245} On the other hand, the major disadvantage of an elemental formulation is its cost, which is reportedly 3–7-
fold higher than that of a polymeric formulation.\textsuperscript{246} The cost of an immune-enhancing formulation is 3–5-fold higher than the cost of an elemental formulation, but whether this leads to better clinical outcomes is unknown.\textsuperscript{247} Both elemental and immune-enhancing formulations have a higher osmolar load than polymeric formulations, which are isomolar, and so may cause diarrhoea. In addition, increased mortality associated with the use of probiotics in patients with AP, observed in the recently published PROPATRIA trial\textsuperscript{248}, has highlighted the need for careful selection of enteral nutrition formulations in current clinical practice as well as in future basic and clinical research.

10.2 Study aim

The aim of this study was to determine and compare the safety, tolerance, and efficacy of all enteral nutrition formulations used in RCTs of patients with AP.

10.3 Methods

10.3.1 Search strategy

Potentially relevant studies were identified using electronic and manual searches. An electronic search was performed in Scopus, Cochrane Controlled Clinical Trials Register, and MEDLINE (searched through PubMed) databases using the terms “acute pancreatitis”, “enteral nutrition”, “glutamine”, “arginine”, “omega-3 fatty acids”, “probiotics”, and “dietary fibre”. Results were limited to trials in humans. The search included literature published from the earliest achievable date of each database to
January 1, 2009. This was also supplemented by scanning the bibliographies of retrieved articles and conference proceedings of selected scientific meetings (Digestive Disease Week, United European Gastroenterology Week, International Pancreatic Association, American Pancreatic Association and European Pancreatic Club) from 2004–2008. All languages and types of publications were considered eligible.

10.3.2 Selection criteria

In order to be included in the systematic review a study had to:

- be a RCT in patients with AP
- compare two different feeding regimens, at least one of which had to include enteral tube feeding (with type of the nutritional formulation used clearly specified)
- report on feeding intolerance (defined as an episode of temporary reduction, stoppage, or withdrawal of feeding) and at least one of the following outcomes: total infectious complications, in-hospital mortality.

Studies investigated the tolerance of oral refeeding or combined enteral and parenteral nutrition or postoperative nutrition were excluded.
10.3.3 Quality assessment

The internal validity of included RCTs was appraised using the five quality criteria of Cochrane collaboration, including method of randomisation, concealment of allocation, blinding, incomplete outcome data, and selective outcome reporting.\textsuperscript{152}

10.3.4 Statistical analysis

Statistics were performed using the Review Manager software (Version 5.0 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and SPSS 14.0 for Windows (SPSS Inc, Chicago, IL, USA). A random-effects model was used to combine the data. Weighted averages were reported as RR with associated 95% CI.\textsuperscript{178} A $p$ value under 0.05 was considered statistically significant. Statistical heterogeneity between studies was evaluated by the Cochran’s $Q$ and $I^2$ tests.

If at least two RCTs directly compared two different enteral nutrition formulations, a direct meta-analysis was performed. Otherwise, to preserve the within-trial randomisation of the originally assigned patient groups, a previously validated method of adjusted indirect meta-analysis was applied (Figure 10.1).
Figure 10.1 Principle of indirect adjusted meta-analysis

Footnote: RCT, randomised controlled trial.

In general terms, to obtain an adjusted indirect estimate of the risk of an event with the use of formulation A versus formulation B from the paired comparisons of formulation A versus formulation C and of formulation B versus formulation C, an overall measure of variation was taken as the sum of the total Chi-squared values from the paired comparisons with n-1 degrees of freedom (where n = total number of included RCTs). Afterwards, a summary RR\(_{AB}\) of the indirect comparison was obtained by taking the difference of the log RR from studies comparing formulation A versus formulation C (lnRR\(_{AC}\)) and from studies comparing formulation B versus formulation C (lnRR\(_{BC}\)):

\[
\text{lnRR}\_AB = \text{lnRR}\_AC - \text{lnRR}\_BC
\]
The exponential of the difference in log RR was taken then as an indirect estimate of the RR. Since all outcomes modelled were undesirable events, an indirectly estimated RR < 1 favoured formulation A, while a RR > 1 favoured formulation B.

A pre-specified sensitivity analysis constrained to trials of patients with predicted severe AP (as defined by the authors) was performed for each study endpoint (feeding intolerance, infectious complications, and mortality).

### 10.4 Results

#### 10.4.1 Identification of studies

The titles and abstracts of 384 identified papers were screened and 348 were excluded after initial screening (Figure 10.2). Sixteen publications were subsequently excluded: four were on refeeding in patients with AP, four were republished in a non-English language, three were conducted in patients with AP after surgery, two compared nasogastric and nasojejunal routes of enteral nutrition, two studied enteral nutrition supplemented with parenteral nutrition, and one used the same study population as in another included RCT. Thus, a total of 20 RCTs met all the inclusion criteria. All included articles were published in peer-reviewed journals.
Figure 10.2 Identification of eligible RCTs.

Abbreviation: RCT, randomised controlled trial
10.4.2 Study characteristics

Among the 20 included RCTs, 19 were single-centre trials\textsuperscript{72–77,88,226,233,234,245,258–265} and there was one multicentre trial\textsuperscript{248}. Patients received an elemental formulation in eight arms of the included trials\textsuperscript{72,74,76,77,226,233,245,261,265}, a polymeric formulation in seven arms\textsuperscript{73,75,88,89,245,263,266}, a fibre-enriched enteral formulation in six arms\textsuperscript{234,248,260,262,264}, enteral nutrition supplemented with probiotics in four arms\textsuperscript{234,248,264,265}, and immunonutrition (glutamine, arginine, and omega-3 fatty acids) in three arms\textsuperscript{260,262,266}.

The 20 RCTs comprised a total of 1070 patients with AP (825 with predicted severe and 245 with predicted mild course of AP). Twelve studies were limited to patients with predicted severe AP only.\textsuperscript{72–77,88,248,260,262–265} Table 10.1 details the study characteristics of included trials.

10.4.3 Quality assessment

Study quality was heterogeneous (Table 10.2). Three trials\textsuperscript{248,262,263} met all five quality criteria (adequate method of randomisation, concealed allocation, blinding, addressing incomplete outcome data, and no selective outcome reporting) and six trials\textsuperscript{72,73,75–77,245} met four quality criteria. Nine trials\textsuperscript{72,73,75–77,245,248,262,263} clearly used a concealed randomisation, and seven trials\textsuperscript{234,248,260,262–265} were blinded. No important baseline differences between treatment groups in the trials were identified.
Table 10.1 Characteristics of included randomised controlled trials

<table>
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<tr>
<th>Reference</th>
<th>Year</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Number of patients</th>
<th>Severe</th>
<th>Mild</th>
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**Abbreviations:** EN, enteral nutrition; PN, parenteral nutrition; PUFA, polyunsaturated fatty acids.
Table 10.2 Methodological quality of included trials

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<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
10.4.4 Publication bias evaluation

The funnel plot for the log RR from the included trials did not show clear asymmetry (Figure 10.3).

Figure 10.3 Funnel plot of included trials

Footnotes: RR, risk ratio; SE, standard error.

10.4.5 Elemental versus polymeric formulation

One RCT directly compared an elemental formulation with a polymeric formulation in 30 patients with mild or severe AP. Given that direct meta-analysis was not possible, the two formulations were compared using the methodology of indirect adjusted meta-analysis. A total of 10 RCTs comprising 428 patients compared elemental and polymeric formulations indirectly, using parenteral nutrition as a
reference treatment. In all patients with AP, the use of an elemental formulation did not result in a significant difference in risk of infectious complications (indirectly estimated RR 0.48; 95% CI 0.06–3.76; p = 0.482) and death (indirectly estimated RR 0.63; 95% CI 0.04–9.86; p = 0.741). The risk of feeding intolerance did not differ significantly between the two formulations (indirectly estimated RR 0.62; 95% CI 0.10–3.97; p = 0.611). These effects were non-significant when only patients with severe AP were considered (Table 10.3).

10.4.6 Fibre-enriched formulation supplemented with probiotics versus fibre-enriched formulation

A total of three RCTs comprising 403 patients directly compared a fibre-enriched formulation supplemented with probiotics and a fibre-enriched formulation only. In all patients with AP, the use of probiotics did not result in a significant difference in the risk of infectious complications (RR 0.71; 95% CI 0.40–1.27; p = 0.250) or death (RR 0.85; 95% CI 0.18–4.14; p = 0.850). The risk of feeding intolerance did not differ significantly between the two formulations (RR 0.69; 95% CI 0.43–1.09; p = 0.110). These effects were non-significant when only patients with severe AP were considered (Table 10.3).
Table 10.3 Pooled estimates and sensitivity analysis

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Severity of acute pancreatitis</th>
<th>Feeding intolerance</th>
<th>Total infectious complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR (95% CI)</td>
<td>p</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>(Semi)-elemental versus polymeric</td>
<td>Mild or severe</td>
<td>0.62 (0.10–3.97)</td>
<td>0.61</td>
<td>0.48 (0.06–3.76)</td>
</tr>
<tr>
<td></td>
<td>Severe only</td>
<td>2.26 (0.32–15.27)</td>
<td>0.41</td>
<td>0.23 (0.03–1.86)</td>
</tr>
<tr>
<td>Fibre-enriched + probiotics versus fibre-enriched</td>
<td>Mild or severe</td>
<td>0.69 (0.43–1.09)</td>
<td>0.11</td>
<td>0.71 (0.40–1.27)</td>
</tr>
<tr>
<td></td>
<td>Severe only</td>
<td>0.69 (0.43–1.09)</td>
<td>0.11</td>
<td>0.79 (0.40–1.56)</td>
</tr>
<tr>
<td>Fibre-enriched + immunonutrition versus fibre-enriched</td>
<td>Mild or severe</td>
<td>1.60 (0.31–8.29)</td>
<td>0.58</td>
<td>0.93 (0.36–2.40)</td>
</tr>
<tr>
<td></td>
<td>Severe only</td>
<td>1.60 (0.31–8.29)</td>
<td>0.58</td>
<td>0.93 (0.36–2.40)</td>
</tr>
</tbody>
</table>

Footnote: *Indirectly estimated RR and its 95% CI; #directly estimated RR and its 95% CI. Abbreviations: CI, confidence interval; RR, relative risk.
10.4.7 Additional studies not included in the meta-analyses

Four RCTs were not included in the above meta-analyses because they were not able to be compared, directly or indirectly, with any other RCTs.\textsuperscript{88,263,265,266} One RCT compared an elemental formulation supplemented with probiotics versus parenteral nutrition.\textsuperscript{265} The use of an enteral feeding formulation resulted in a significantly reduced rate of septic complications (eight of 36 (22\%) versus 21 of 38 (55\%) patients; p = 0.008) and no difference in mortality (no deaths in both groups). Another trial compared a fibre-enriched formulation with a fibre-free formulation and demonstrated no difference in infectious complications (two of 15 [13\%] patients in each group) or mortality (two of 15 [13\%] patients versus four of 15 [27\%] patients).\textsuperscript{263} All patients tolerated the fibre-enriched formulation, whereas feeding intolerance was observed in two patients who received the fibre-free formulation. One trial compared a polymeric formulation with no nutrition.\textsuperscript{88} There was no difference between the groups with regard to rate of infectious complications or mortality. A final RCT compared a polymeric formulation supplemented with n-3 polyunsaturated fatty acids with a polymeric formulation only.\textsuperscript{266} There was no significant difference between the groups with regard to rate of infectious complications (five of 14 [36\%] versus seven of 14 [50\%] patients) or mortality (one of 14 [7\%] versus two of 14 [14\%] patients).
10.5 Discussion

This is the first systematic literature review that aimed to define the optimal enteral nutrition formulation in patients with AP. The major finding here is that the use of a polymeric, in comparison with an elemental, enteral nutrition formulation was not associated with a statistically significant difference in tolerance of feeding, or risk of infectious complications and mortality. In addition, the present systematic review shows that a fibre-enriched formulation may be safely administered in patients with AP and its supplementation with immunonutrition or probiotics does not improve clinically meaningful outcomes.

The present study further questions the “pancreas rest” concept, which is perhaps the oldest postulate in the management of AP. As discussed in the preceding chapters, a cornerstone of this concept is that avoidance or minimisation of the pancreatic enzyme secretory response might prevent exacerbation of the acute inflammatory process in the pancreas. At least in theory, this may be achieved by administration of a feeding formulation that does not require pancreatic enzymes for absorption (e.g., amino acids or oligopeptides). This was the reason why use of polymeric and fibre-enriched formulations was avoided for decades. However, only two prospective studies showed that a polymeric formulation increases pancreatic enzyme secretion into the duodenum in comparison with an elemental formulation, and both of these studies were conducted in healthy volunteers. Conversely, a RCT of patients undergoing resection of the pancreas showed that a polymeric formulation did not increase pancreatic secretion compared with an elemental formulation. The latter finding supports the results of the present study that demonstrated no increase in
adverse effects with the use of polymeric and fibre-enriched formulations. Although one might argue that such an inference is premature and it is necessary to wait for a definitive RCT, a power calculation shows that this is no simple undertaking. An adequately powered RCT would need to enrol 1959 patients per study arm in order to demonstrate a 1.5% absolute reduction in the risk of death between the groups with 80% power and two-sided $\alpha = 0.05$. Such a sample size appears to be unrealistically large, even for a multicentre trial.

It is also worth noting that elemental and polymeric feeding formulations were rigorously compared over the last two decades in a number of RCTs in patients with active Crohn’s disease, which is perhaps the only disease, apart from AP, in which enteral feeding is used as an established key element of treatment. By 1995, four RCTs were published, and subsequent meta-analyses failed to demonstrate a difference in efficacy between elemental and polymeric formulations.\textsuperscript{269} By 2007, a total of 10 RCTs were published, but a Cochrane systematic review still found no difference in the induction of remission of active Crohn’s disease when different formulations were compared.\textsuperscript{270} Hence it is argued that the use of polymeric feeding formulations is safe in patients with AP, and the research community may now focus on other issues in AP nutrition, which will be discussed in the following chapter (Chapter 11).

10.6 Limitations

This study has a number of limitations. They include the small sample size of most studies and the poor methodological quality of some trials. The results of indirect adjusted meta-analysis may not fully correspond to those of meta-analysis of direct
head-to-head RCTs. However, the methodology of indirect adjusted meta-analysis was previously validated by different authors and applied in a number of clinical settings.\textsuperscript{249,271,272} One should also be aware that wide CIs for some comparisons do not completely rule out the possibility of big increases in risk, or big decreases in risk. Also, the fibre content of feeding formulations varied in type of fibre and this may have had a different effect on the intervention (probiotics, immunonutrition) in the included trials. To address this issue, a random-effect model was used to meta-analyze the data. Finally, given that a series of physiological studies showed that only jejunal feeding avoids stimulating pancreatic secretion, it can be argued that polymeric and fibre-enriched formulations did not cause a harmful effect because feeding was nasojejunal in the majority of trials.\textsuperscript{121} However, it is worth noting that only enteral feeding delivered into the mid to distal part of jejunum (i.e., at least 60 cm beyond the ligament of Treitz) was shown to be non-stimulatory.\textsuperscript{273} Such feeding is technically challenging and available in only a few dedicated centres. It is most likely that patients received proximal jejunal feeding in the included trials, ruling out the tube position as the reason for non-stimulation.

10.7 Conclusion

The present systematic review and meta-analysis of RCTs shows that the use of a relatively inexpensive polymeric over a more costly elemental formulation does not result in reduced feeding tolerance in patients with AP. Also, a polymeric formulation appears to be as beneficial as an elemental formulation in reducing the risk of infectious complications and mortality in patients with AP. By contrast, there is no evidence to date to justify the use of immunonutrition and probiotics in patients with
AP. The promising potential of a fibre-enriched formulation in improving the
tolerance of enteral feeding should be investigated in an adequately powered
randomised study.
SUMMARY OF PART II

Enteral tube feeding is one of the most effective approaches in the management of AP. The latest guidelines recommend it in the form of nasojejunal infusion of an elemental formulation in patients with predicted severe AP. In Chapter 7, the safety, tolerance, and efficacy of nasogastric tube feeding were systematically assessed. The evidence base comprised five clinical studies, including three RCTs of nasogastric versus nasojejunal feeding. Nasogastric feeding was well tolerated in more than 80% of patients, and there was no difference between the nasogastric and nasojejunal routes in terms of risk of feeding intolerance, infectious complications, and mortality. These data, coupled with the practical advantages of nasogastric versus nasojejunal tube feeding, determined use of the former as the intervention in the EFAP trial.

The EFAP trial was designed as the first RCT of nasogastric tube feeding in patients with mild to moderate AP. The hypothesis was that the early (within 24 hours of hospital admission) use of enteral tube feeding, when compared with a conventional NBM regimen, leads to better tolerance of subsequent oral refeeding and, possibly, a reduced length of hospitalisation (Chapter 8). The results of the interim analysis presented in Chapter 9 showed that early nasogastric feeding significantly reduced the risk of pain relapse after introduction of oral refeeding but not the total length of hospital stay. In addition, the intensity and duration of initial abdominal pain as well as the need for opiates were significantly reduced with use of early nasogastric feeding. The EFAP trial provided the first direct evidence of a possible benefit of enteral tube feeding in patients with mild to moderate AP. It also added to the growing controversy...
surrounding the “pancreas rest” concept in AP by showing the safety of nasogastric feeding, at least when used as reported, in all patients enrolled in the intervention arm.

In addition to the site of enteral tube feeding, another important aspect of the “pancreas rest” concept is the type of formulations used for enteral nutrition. It is believed that only an elemental formulation is non-stimulatory, and on this basis such formulations are widely advocated by the current guidelines. Chapter 10 explored the safety, tolerance, and efficacy of other formulations, such as polymeric formulations, immunonutrition, probiotics, and fibre-enriched formulations. A total of 20 RCTs comprising more than 1000 patients with AP were analysed. It was shown that, contrary to popular opinion, use of a polymeric formulation does not increase the risk of feeding intolerance, infectious complications, or mortality in comparison with an elemental formulation. Also, the use of probiotics or immunonutrition appears to be unjustified in patients with AP. A fibre-enriched formulation appears to be safe and has a potential to mitigate diarrhoea, but an adequately powered RCT is warranted before this formulation is recommended for routine clinical practice.
Chapter 11

FURTHER FRONTIERS

Findings from the work in this thesis have highlighted a number of areas that require further investigation. This chapter presents some of the possible future research directions pertinent to classifying the severity of AP and nutritional management of patients with this disease.

11.1 Research on severity of acute pancreatitis

11.1.1 Further interrogation of definitions of local determinants of severity

As identified in Chapter 5, the global survey of pancreatologists indicated that there is no agreement as to the extent of hypoperfusion required to diagnose necrosis. One third of the survey respondents considered that the diagnosis of necrosis on initial (early) CT required detection of any hypoperfusion and another one third considered that it needed hypoperfusion of more than 30% of the pancreas. Further radiological studies should investigate the optimal criteria for diagnosis of pancreatic necrosis on early CT scan. This is important for determining the real prevalence of pancreatic necrosis and standardising the reports of clinical studies in AP.

While the majority of patients with necrotising pancreatitis develop both pancreatic necrosis and peripancreatic necrosis, it is known that some patients develop pancreatic necrosis alone or peripancreatic necrosis alone. There is a growing body of
evidence that peripancreatic necrosis alone contributes to severity, but no study has directly compared it with pancreatic necrosis alone. As identified in Chapter 5, there is no agreement among the leading pancreatologists about the relative importance of pancreatic necrosis and peripancreatic necrosis as determinants of severity. Therefore, a clinical study is warranted to compare the outcomes of patients with peripancreatic necrosis alone versus those with pancreatic necrosis alone.

11.1.2 Further interrogation of definitions of systemic determinants of severity

While the importance of OF in patients with AP has been well recognised since the Marseilles classification of severity in 1984, recent studies have demonstrated that the duration of OF rather than its mere presence or absence is of importance. However, those studies used an arbitrary threshold of three consecutive days or more to define persistent OF. Further research is needed to establish a minimal clinically meaningful duration of OF. In particular, it is worth establishing the risk of mortality in patients with AP who have OF for two consecutive days or more, and whether it is significantly lower in comparison with those who have it for three consecutive days or more.

As identified in Chapter 5, the global survey of pancreatologists indicated that there is no agreement as to the method used to diagnose OF. Half of the respondents prefer to diagnose OF separately using a certain threshold and half prefer to use a composite score (e.g., SOFA). The use of a composite organ dysfunction score seems favourable from a research perspective, but further studies have to investigate whether it presents any advantages in routine clinical practice.
Further studies are also warranted to investigate the effect of timing of OF on outcomes in AP, in particular whether “early” OF is more ominous in comparison with “late” OF. As discussed in Chapter 6, the three single-centre studies available in the literature are inconclusive and suffer from several important flaws.\textsuperscript{109,166,167} Further studies, preferably prospective studies from multiple (international) centres, are warranted to answer this important question.

11.1.3 Prospective validation of determinant-based classification of severity

The determinant-based classification of AP severity has been presented in Chapter 6. The logical question to be raised is whether the new classification of severity that comprises four categories (“mild”, “moderate”, “severe”, and “critical”) contributes more than the traditional binary approach (“mild” and “severe”) in the clinical management of patients with AP. The answer to this will have to be determined by prospective validation studies in which the classification is applied to the care of patients, to plotting of the clinical course, and to the audit of clinically meaningful outcomes.
11.2 **Research on nutrition in acute pancreatitis**

11.2.1 Further randomised trials of nasogastric tube feeding in patients with acute pancreatitis

As identified in Chapter 7, nasogastric tube feeding appears to be safe and well tolerated in the vast majority of patients with AP. However, the evidence base is limited, with only five rather small RCTs of nasogastric tube feeding (including the EFAP trial presented in Chapters 8 and 9) available in the literature (Figure 9.4). Larger-scale RCTs looking at the effect of nasogastric tube feeding in patients with AP are desirable. In particular, a large-scale RCT is needed to investigate whether nasogastric tube feeding can prevent the progression of severity in patients with AP. As discussed in Chapter 8, the potential benefits which enteral nutrition may offer are dual, i.e., improvement in tolerance of oral refeeding and prevention of progression in severity of AP. The former benefit has been confirmed by the EFAP trial (presented in Chapter 9). However, that trial was not sufficiently powered to detect a statistically significant difference in progression of severity between the studied groups (Figure 11.1). A further RCT should also determine whether a decrease in the risk of pain relapse results in a statistically significant reduction in length of hospitalisation and, eventually, overall cost of treatment.
Figure 11.1 Hypotheses confirmed in EFAP trial (solid line) and hypotheses that need to be evaluated (dashed line) in further RCTs of nasogastric tube feeding in patients with acute pancreatitis.
A particular emphasis in future studies must be in relation to study populations. Given that the use of predictive criteria of severity was advocated by the Atlanta classification\textsuperscript{19}, the majority of RCTs conducted to date have enrolled patients on the basis of various criteria of predicted severity with different thresholds (Ranson score $> 3$, APACHE II score $> 8$, APACHE II score $> 7$, APACHE II score $> 6$, CRP $> 150$, CRP $> 120$). While this approach was helpful in determining the principal benefits of enteral delivery of nutrition in patients with AP, the downside is that the actual population of patients with AP which benefits from enteral nutrition is largely unknown because of misclassification error. That is why future studies in the field should employ the new classification of severity, which is based on actual determinants of severity, to enrol patients in the trial and assess the effect of treatment. This will ensure that nutritional management is tailored to patients with each category of actual severity. In particular, RCTs are needed to investigate the optimal nutritional management in the most challenging patients, i.e., those with severe and critical AP. Given that these patients are not prevalent in routine practice, a multicentre (international) collaboration will be required.

11.2.2 Pilot randomised trial of early nasogastric tube feeding versus oral feeding ad libitum in patients with mild to moderate acute pancreatitis

The benefits of early (within 24 hours of hospital admission) nasogastric tube feeding in comparison with a NBM regimen were demonstrated in the EFAP trial (Chapter 9). This randomised trial showed that early administration of nasogastric tube feeding is safe and does not exacerbate the course of AP. Furthermore, the use of nasogastric tube feeding significantly reduces the intensity and duration of initial pain and
prevents pain relapse after oral refeeding. At the same time, a recent RCT from Sweden compared early (within 24 hours of hospital admission) oral feeding ad libitum with NBM and showed that oral feeding does not exacerbate the course of AP and even reduces the total length of hospital stay, but no significant effect on the intensity and duration of initial pain was observed. A pilot RCT is now warranted to compare directly the interventions used in the two trials, i.e., nasogastric tube feeding and oral feeding ad libitum (Figure 11.2). A RCT of this design would be of both practical and theoretical importance. From a practical perspective, it would help to determine the optimal early feeding regimen in patients with AP. From a theoretical perspective, it would provide a definitive answer as to whether the “pancreas rest” concept can be buried or not (discussed in detail in Chapter 9).
Figure 11.2 Place of proposed pilot RCT of early nasogastric tube feeding versus oral feeding ad libitum in the literature

Footnotes: NBM, nil-by-mouth; NG, nasogastric tube feeding; RCT, randomised controlled trial.
11.2.3 Definitive randomised controlled trial of fibre-enriched enteral nutrition in acute pancreatitis

As identified in Chapter 10, enteral nutrition is associated with a relatively high rate of adverse effects in patients with AP, in particular diarrhoea. A meta-analysis of 13 RCTs comparing fibre-enriched and fibre-free enteral feeding formulations showed a significant reduction of diarrhoea in patients receiving the former.\textsuperscript{274} This makes fibre-enriched formulations a promising and clinically relevant approach to minimising the risk of diarrhoea in patients with AP. To date, the effect of fibre has been evaluated in only one RCT in patients with predicted severe AP.\textsuperscript{263} That study demonstrated no cases of diarrhoea in 15 patients receiving a fibre-enriched formulation, compared with two of 15 patients receiving a fibre-free formulation. Taking into account the limited sample size of the study, an adequately powered RCT of a fibre-enriched versus fibre-free formulation in patients with AP appears to be warranted.

The call for such a trial was also supported by the eagerly awaited and very disappointing results of the PROPATRIA trial.\textsuperscript{248} A common interpretation of this study is that the use of probiotics in patients with predicted severe AP led to a significantly increased risk of intestinal ischaemia, multiple OF, and mortality. However, this is not entirely correct because, in fact, the intervention group in the PROPATRIA received a fibre-enriched formulation supplemented with six strains of probiotics whereas the control group received a fibre-enriched formulation alone. Therefore, one can only conclude from this study that the given combination of probiotics and fibres was harmful, whereas the fact that mortality was only 6% in the
control group and no cases of intestinal necrosis were observed, shows that a fibre-enriched formulation is safe in patients with AP.

11.2.4 Further studies on immunonutrition in acute pancreatitis

As identified in chapter 10, only three RCTs on the use of immunonutrition are available in the literature, and they did not demonstrate any clinical beneficial effect of enteral nutrition enriched with glutamine, arginine, and/or omega-3 fatty acids when compared with standard enteral nutrition in patients with AP. At first sight, given that the sample sizes of all the RCTs were too small, it seems that no definitive conclusions can be drawn from them. Nevertheless, an authoritative meta-analysis of several hundred critically ill and elective surgery patients, which was greater in terms of study population, found a statistically significant benefit of immunonutrition (reduced risk of infectious complications) only in the subgroup of patients who received a high-arginine-content formula. However, excessive arginine supplementation could have a potentially damaging effect on the pancreas, probably due to the excessive production of nitric oxide. It is also known that administration of omega-3 fatty acids decreases antioxidant capacity. Nevertheless, the relevance of these experimental observations is difficult to evaluate in the clinical setting because immunonutrition is usually administered in a compound and it is hard to ascribe a beneficial or harmful effect of an immunonutritional formulation to any single immune-enhancing agent. Thus, further clinical and animal studies should focus on individual immune-enhancing agents, of which glutamine seems to have the greatest beneficial potential in the setting of AP.
11.2.5 Pilot study of antioxidant-enriched enteral nutrition in acute pancreatitis

Although oxidative stress has been implicated as an important factor in the pathogenesis of AP for nearly three decades, the therapeutic effect of antioxidants in patients with AP has been investigated in only a few inconclusive RCTs. The only high-quality trial enrolled 43 patients with predicted severe AP (APACHE II score ≥ 8 within 48 hours of admission) and showed no benefit of intravenous antioxidant therapy (n-acetylcysteine, selenium, vitamin C) administered for 7 days. Moreover, the study was terminated at the time of interim analysis because some data suggested that the intervention might even be harmful. Following the publication of this study in 2007, some authors rushed to conclude that “the book on the antioxidant story in the treatment of AP has closed”. However, while the trial clearly showed that the given combination of antioxidants is not effective in patients with AP when administered intravenously, it is quite possible that antioxidants administered via another route will be beneficial. In particular, there is a growing body of clinical evidence from other disease settings that supplementation of enteral nutrition with antioxidants might be beneficial. Given that the benefits of standard enteral nutrition in patients with AP are well proven, the use of antioxidant-enriched enteral nutrition may be a sensible direction of clinical research in AP.
The frontiers in clinical management of patients with AP continue to advance. The findings presented in this thesis have contributed to the two important areas - classifying the severity and use of enteral nutrition in AP.

The importance of accurate classification of severity in AP has been emphasised and the deficiencies in the classifications used to date have been highlighted, in particular the need to have a clinically and epidemiologically sound conceptual framework for classifying severity. The determinant-based classification has been developed based on the concept of causal inference. This classification of severity reflects, through its four categories, clinically relevant changes that occur in individual patients, uses widely accepted and unambiguous terms, can be applied in both early and late phases of AP, and will prove useful in tracking individual patients and comparing groups of patients.

There is ample evidence in the literature that the use of nasojejunal tube feeding improves outcomes in patients with predicted severe course of AP. This work has demonstrated the safety and efficacy of nasogastric tube feeding in these patients. Furthermore, for the first time, it has been shown in a randomised trial that early nasogastric tube feeding may have benefits for patients with actual mild to moderate AP. Lastly, optimal enteral feeding formulations have been determined based on the best available data.
Further expansion of frontiers in clinical management of AP represents a formidable opportunity for improving patient care. As long ago as 1928, Bertrand Russell wrote “The extent to which beliefs are based upon evidence is very much less than believers suppose”. This still pretty much holds true today in the management of the most frequent disease of the pancreas.
### Survey on Classification of Severity of Acute Pancreatitis

#### 1. ABOUT YOU

- **1. What is your country of residence?**

- **2. What is your specialty?**
  - General Surgery
  - Gastroenterology
  - Intensive Care
  - Radiology
  - Other (please specify)

- **3. Approximately how many patients did you manage with acute pancreatitis in the last 12 months?**
  - < 20
  - 20-50
  - > 50
Survey on Classification of Severity of Acute Pancreatitis

* 4. We are convening a consensus meeting on classification of severity of acute pancreatitis during the International Association of Pancreatology meeting in February 2011 (www.iap2011.org).

A consensus document will be published in Pancreatology after the meeting.

Would you like to collaborate on this document?

☐ Yes
☐ No
Survey on Classification of Severity of Acute Pancreatitis

2. LOCAL COMPLICATIONS

* 1. Would you make a diagnosis of pancreatic necrosis if the area of hypoperfusion on contrast-enhanced CT, performed within the first few days, is less than 30%? Tick one answer.
   - No
   - Yes, when the area is more than 20%
   - Yes, when the area is more than 10%
   - Yes, when the area is more than 5%
   - Yes, when there is any area of hypoperfusion

* 2. In your opinion, which of the following is true with regard to sterile pancreatic parenchymal and peripancreatic fat necrosis? Tick one answer.
   - Pancreatic necrosis is, in general, associated with worse outcome (e.g., increased length of hospital stay) than peripancreatic necrosis
   - Peripancreatic necrosis is, in general, associated with worse outcome (e.g., increased length of hospital stay) than pancreatic necrosis
   - Pancreatic and peripancreatic necrosis are, in general, associated with a similar outcome
   - I do not have an opinion on this
Survey on Classification of Severity of Acute Pancreatitis

* 3. With respect to sterile (peri)pancreatic lesions, which of the following do you think represents moderate (rather than mild) severity of acute pancreatitis? Tick one or more answers.

☐ Peripancreatic fluid collection (within the first few days after onset)
☐ Peripancreatic fluid collection with a well-defined wall that does not contain necrosis
☐ Peripancreatic collection without a well-defined wall that contains fluid and necrosis
☐ Peripancreatic collection with a well-defined wall that contains fluid and necrosis

☐ None
☐ I do not have an opinion on this

* 4. With respect to infected pancreatic lesions, which of the following is, in general, associated with a mortality risk similar to infected pancreatic necrosis? Tick one answer.

☐ Infected pancreatic collection without a well-defined wall that contains fluid and necrosis
☐ Infected pancreatic collection with a well-defined wall that contains fluid and necrosis

☐ Both
☐ Neither
☐ I do not have an opinion on this

5. In your opinion, is the extent of sterile pancreatic necrosis related to the risk of mortality? (For example, do patients with 70% parenchymal necrosis have, in general, a higher risk of mortality than those with 40% parenchymal necrosis?)

☐ Yes
☐ No
Survey on Classification of Severity of Acute Pancreatitis

3. SYSTEMIC COMPLICATIONS

* 1. In your opinion, which organ systems should be assessed to define organ failure in patients with acute pancreatitis? Tick one or more answers.

☐ Cardiovascular
☐ Hematologic
☐ Hepatic
☐ Neurologic
☐ Renal
☐ Respiratory
☐ Other (please specify)

2. In your opinion, how long should the same organ failure be recorded to define persistent organ failure? Tick one answer.

☐ At least once during each of 2 consecutive 24h periods
☐ At least once during each of 3 consecutive 24h periods
☐ At least once during each of 4 consecutive 24h periods
☐ At least once during each of 6 consecutive 24h periods

* 3. In your opinion, how should a single organ failure be defined in patients with acute pancreatitis? Tick one answer.

☐ On the basis of a defined threshold for each organ system (e.g., creatinine level of more than 177umol/L [2 mg/dL] to diagnose renal failure)
☐ On the basis of a scoring system that provides up to 4 different levels of organ dysfunction (e.g., SODA score where you need ≥ 2 points for renal dysfunction to diagnose renal failure)
Survey on Classification of Severity of Acute Pancreatitis

4. In your opinion, how many organ systems should be failed at the same time to define multiple organ failure? Tick one answer.

- 2 or more
- 3 or more
- 4 or more
- 5 or more
Survey on Classification of Severity of Acute Pancreatitis

4. CLASSIFICATION OF SEVERITY

*1. The Atlanta classification of the severity of acute pancreatitis (Arch Surg, 1993) stratifies patients into mild and severe pancreatitis, as outlined in the table below.

Do you think that this is adequate for modern clinical practice and clinical research?

☐ Yes
☐ No

<table>
<thead>
<tr>
<th>SEVERITY CATEGORY</th>
<th>LOCAL Pancreas Morphology</th>
<th>SYSTEMIC Distant Organ Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>No local complications</td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No organ failure</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Local complications</td>
<td>AND/OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organ failure</td>
</tr>
</tbody>
</table>

*2. A new approach to the classification of severity, based on dynamic changes of certain local and systemic complications as well as interaction between them during the course of acute pancreatitis, has recently been published (Am J Gastroenterol, 2010). The concept of the four categories of severity is outlined in the table below.

Do you conceptually support this classification of severity?

☐ Yes
☐ No
**Survey on Classification of Severity of Acute Pancreatitis**

<table>
<thead>
<tr>
<th>SEVERITY CATEGORY</th>
<th>LOCAL Pancreas Morphology</th>
<th>SYSTEMIC Distant Organ Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>No local complications</td>
<td>AND No organ failure</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Sterile (peri)pancreatic complications</td>
<td>OR Transient and/or single organ failure</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Infectious (peri)pancreatic complications</td>
<td>OR Persistent and/or multiple organ failure</td>
</tr>
<tr>
<td>CRITICAL</td>
<td>Infectious (peri)pancreatic complications</td>
<td>AND Persistent and/or multiple organ failure</td>
</tr>
</tbody>
</table>

*N.B. Please note that this table outlines the conceptual framework only. The definitions of each term will be discussed at the Consensus Meeting during the International Association of Pancreatology meeting in February 2011 and your opinion (as expressed in the sections 2 and 3 of this survey) will be taken into account.*
Survey on Classification of Severity of Acute Pancreatitis

* 3. Would you agree or disagree that the new classification system reflects clinically important changes in patients with acute pancreatitis better and is more useful in clinical practice than the Atlanta classification? Tick one answer.

- Strongly agree
- Agree
- Somewhat agree
- Neither agree nor disagree
- Somewhat disagree
- Disagree
- Strongly disagree

* 4. Would you agree or disagree that the new classification system selects patients for clinical studies better and reports on their severity more precisely than the Atlanta classification? Tick one answer.

- Strongly agree
- Agree
- Somewhat agree
- Neither agree nor disagree
- Somewhat disagree
- Disagree
- Strongly disagree
Survey on Classification of Severity of Acute Pancreatitis

5. Please use the box below if you want to comment on the concept of the four categories of severity.
Appendix 2. Programme of the symposium on classification of acute pancreatitis severity

IAP SYMPOSIUM ON
CLASSIFICATION OF ACUTE PANCREATITIS SEVERITY

**Moderators:** Santhi Vege (USA), John Windsor (New Zealand)

Thursday, 10 February 2011
Hall C (Vater), International Convention Center, Le Meridien, Cochin

**PROGRAMME**

13.00 – 13.10 Introduction and why we need to classify the severity of acute pancreatitis

Santhi Vege (USA)

**THE CLASSIFICATION OF SEVERITY OF ACUTE PANCREATITIS**

13.10 – 13.25 Development and requirements of a conceptual framework for the classification of the severity of acute pancreatitis

Max Petrov (New Zealand)

13.25 – 13.35 Justification for a ‘moderate’ category

Rup Talukdar (India)

13.35 – 13.45 Justification for a ‘critical’ category

John Windsor (New Zealand)

13.45 – 14.10 Discussion
LOCAL DETERMINANTS OF SEVERITY

14.10 – 14.20 Pancreatic and peripancreatic necrosis: Features of prognostic significance

Tooru Shimosegawa (Japan)

14.20 – 14.30 (Peri)pancreatic infection: Markers and measures

Bettina Rau (Germany)


Hein Gooszen (The Netherlands)

14.40 – 15.05 Results of global survey and Discussion

SYSTEMIC DETERMINANTS OF SEVERITY

15.05 – 15.15 Organ failure: Timing, measures and prognostic significance

Pramod Garg (India)

15.15 – 15.25 Factors associated with mortality in patients with organ failure: International multicenter study

Max Petrov (New Zealand)

15.25 – 15.45 Results of global survey and discussion

CONCLUSION

15.45 – 15.55 Summary of the meeting and key issues

John Windsor (New Zealand)

15.55 – 16.00 Consensus on the classification of severity: the way forward

Santhi Vege (USA)
Appendix 4. Clinical care pathway used in the EFAP trial

A CLINICAL CARE PATHWAY FOR

ACUTE PANCREATITIS

PLEASE READ THIS FIRST

Use this pathway if:

- Pain suggesting acute pancreatitis
- Serum amylase and/or lipase at least 3x normal

Stop using this pathway if:

- No abdominal pain
- No use of analgesics
- Normal diet tolerated

- Nurses (WHITE zones) and doctors (GREY zones) to use it.
- You must sign your entry, as indicated.
# Fill This In On Admission

## Admission Check

<table>
<thead>
<tr>
<th>Admission date</th>
<th>Patient's ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>/</strong>/20</td>
<td>□ NZ European □ Maori</td>
</tr>
<tr>
<td></td>
<td>□ Chinese □ Indian</td>
</tr>
<tr>
<td></td>
<td>□ Pacific Islands □ Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfer from other hospital</th>
<th>Time from first symptoms to hospital admission in hours:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ No</td>
<td>On waiting list for cholecystectomy</td>
</tr>
<tr>
<td>□ Yes</td>
<td>Known gallstone carrier for at least 4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biliary colic (RUQ pain for at least 30 min but less than 6h)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Never</td>
<td>Yes</td>
</tr>
<tr>
<td>□ Yes, prior to (during) this admission only</td>
<td></td>
</tr>
<tr>
<td>□ Yes, multiple (there was a pain-free interval of at least 7 days)</td>
<td></td>
</tr>
<tr>
<td>Reason: □ GP delay □ Patient delay No. of colics</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aetiology of acute pancreatitis</th>
<th>Number of previous admissions for AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Biliary</td>
<td>□ No previous admissions</td>
</tr>
<tr>
<td>□ Trauma</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ Other</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ Alcohol</td>
<td>□ ≥3</td>
</tr>
<tr>
<td>□ Post-ERCP</td>
<td></td>
</tr>
<tr>
<td>□ Unknown</td>
<td></td>
</tr>
</tbody>
</table>

ASA - American Society of Anaesthesiologists co-morbidity class

<table>
<thead>
<tr>
<th>□ I (no organic, physiologic, or psychiatric disturbance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ II (a well-controlled disease of one body system, no functional limitations, e.g. controlled hypertension or diabetes without systemic effects, mild obesity, pregnancy)</td>
</tr>
<tr>
<td>□ III (a controlled disease of more than one body system or some functional limitations, e.g. poorly controlled hypertension, morbid obesity, COPD with intermittent symptoms)</td>
</tr>
<tr>
<td>□ IV (at least one severe disease that is a constant threat to life or at end stage, e.g. unstable angina, symptomatic COPD, symptomatic heart failure)</td>
</tr>
</tbody>
</table>

Specific co-morbidities

<table>
<thead>
<tr>
<th>□ Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Obesity (BMI &gt;35)</td>
</tr>
<tr>
<td>□ Pregnancy</td>
</tr>
<tr>
<td>□ Viral hepatitis</td>
</tr>
<tr>
<td>□ HIV</td>
</tr>
</tbody>
</table>

Tests to be ordered

<table>
<thead>
<tr>
<th>Amylase pancreatic</th>
<th>□ Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>□ Yes</td>
</tr>
<tr>
<td>CRP</td>
<td>□ Yes</td>
</tr>
<tr>
<td>LFTs</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Blood culture (if Temp &gt; 38°C)</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Serum LDH</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Blood urea</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Blood lactate</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>□ Yes</td>
</tr>
</tbody>
</table>

Doctor's Name:________________________ Signature:________________________
**PREDICTION OF SEVERITY**

(Complete within 24 hours of hospital admission)

**Harmless Acute Pancreatitis Score**
- No rebound tenderness and/or guarding  □ (1 point)
- Initial Hct < 43% for males and < 40% for females □ (1 point)
- Serum creatinine < 177 umol/L □ (1 point)

*If HAPS = 3 then the patient is likely to have mild acute pancreatitis.*

**Modified Glasgow Score**
- Leukocytes > 15 x 10^9/L □ (1 point)
- Glucose* > 10 mmol/L □ (1 point)
- Serum LDH > 600 IU/L □ (1 point)
- Age > 55 years □ (1 point)
- Blood urea > 16 mmol/L □ (1 point)
- Arterial PaO₂ < 8 kPa □ (1 point)
- Calcium* < 2.6 mmol/L □ (1 point)
- Albumin < 32 g/L □ (1 point)

* * not adjusted
** for non-diabetics

*If Glasgow Score ≥ 3 then patient has predicted severe acute pancreatitis – consider transfer.*

**Bedside Index for Severity in Acute Pancreatitis**
- Blood urea > 8.9 mmol/L □ (1 point)
- Age > 60 years □ (1 point)
- Impaired mental status □ (1 point)
- Pleural effusion on CXR □ (1 point)

*If RISAP Score ≥ 3 then mortality > 9% – consider transfer.*

**INITIAL ASSESSMENT OF ORGAN DYSFUNCTION**

(Complete within 24 hours of hospital admission)

**Multiple Organ Dysfunction Score**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong> (PaO₂, kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 11.2</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>8.4-11.2</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>5.6-8.3</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9-5.5</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2.8</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong> (serum creatinine, μmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 134</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>134-169</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>170-310</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>311-439</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>&gt; 439</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong> (systolic blood pressure, mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 90</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>&lt; 90, fluid responsive</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>&lt; 90, fluid unresponsive</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>&lt; 30, pH &lt; 7.3</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>&lt; 30, pH &lt; 7.2</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
</tbody>
</table>

*If a score of ≥ 2 in at least one of the organ systems then consider HDU/ICU admission.*
<table>
<thead>
<tr>
<th>Laboratory tests to be ordered</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase pancreatic</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>FBC</td>
<td>Yes</td>
<td>LFTs (if biliary etiology)</td>
<td>Yes</td>
</tr>
<tr>
<td>CRP</td>
<td>Yes</td>
<td>Blood glucose (if was elevated)</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood lactate</td>
<td>Yes</td>
<td>Blood culture (if Temp &gt; 38°C)</td>
<td>Yes</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient Education regarding:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Alcohol cessation ☐ Smoking cessation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Additional Clinical Notes:**

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
DAY ___ / ___ / 20

Global judgment of any change in the patient’s overall symptoms
Please make a global clinical judgment of overall change in the severity of the patient’s symptoms compared with 24 hours previously (circle the number on the 15 point scale)

<table>
<thead>
<tr>
<th></th>
<th>-7</th>
<th>-6</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
<th>+4</th>
<th>+5</th>
<th>+6</th>
<th>+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>-A very great</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>-Better</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>-Almost the same, hardly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>-worse at all</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>-A very great</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>-Better</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

Multiple Organ Dysfunction Score

<table>
<thead>
<tr>
<th></th>
<th>SCORE (0 to 4 points for each organ system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>0</td>
</tr>
<tr>
<td>(PaO₂/kPa)*</td>
<td>&gt; 11.2</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
</tr>
<tr>
<td>(serum creatinine, umol/l)</td>
<td>&lt; 134</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>(systolic blood pressure, mmHg)</td>
<td>0</td>
</tr>
</tbody>
</table>

If a score of ≥ 2 in at least one of the organ systems then consider ICU/ICU admission

Total Score

Doctor’s name:

Management

<table>
<thead>
<tr>
<th>Analgesia</th>
<th>Doctor</th>
<th>Nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia prescribed:</td>
<td>Yes</td>
<td>AM PM NIGHT</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>IV</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PCA</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Hydration

<table>
<thead>
<tr>
<th>IV Fluids prescribed:</th>
<th>Yes</th>
<th>AM PM NIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Crystalloid Vol. 24h (mL)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rate (mL/h)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

| Colloid Vol. 24h (mL) | Yes | AM PM NIGHT |
| Rate (mL/h)           | No  | No          |

<table>
<thead>
<tr>
<th>Urine output recorded</th>
<th>Yes</th>
<th>AM PM NIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Nutrition

| Nil by mouth | Yes | AM PM NIGHT |
| Oral - fluids only | No | No |
| Oral - light diet | Yes | No |
| Oral - full diet | No  | Yes         |
| Refer to dietitian | Yes | No |
| PN               | No  | Yes         |
| NG tube feeding   | Yes | No          |
| NO tube feeding   | No  | Yes         |

Other Medications

<table>
<thead>
<tr>
<th>As per Drug Chart</th>
<th>Yes</th>
<th>AM PM NIGHT</th>
</tr>
</thead>
</table>

Signatures

Signature:
### SPECIAL INVESTIGATIONS
(Complete this as the investigations are ordered during the hospital admission)

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Date</th>
<th>Findings/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>/20</td>
<td>□ Pleural effusion</td>
</tr>
<tr>
<td>Abdominal US</td>
<td>/20</td>
<td>□ No stones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Choledolithiasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Choledocholithias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ CBD diameter: mm</td>
</tr>
<tr>
<td>MRCP</td>
<td>/20</td>
<td>□ No stones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Choledolithiasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Choledocholithias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ CBD diameter: mm</td>
</tr>
<tr>
<td>Initial CT scan</td>
<td>/20</td>
<td>□ No necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Pancreatic necrosis, %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Peripancreatic necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Pancreatic/peripancreatic collections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Gas/air</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ CTSI (Balthazar) score:</td>
</tr>
<tr>
<td>Repeated CT scan</td>
<td>/20</td>
<td>□ Global better</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Global worse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ CTSI (Balthazar) score:</td>
</tr>
<tr>
<td>FNA</td>
<td>/20</td>
<td>□ Sterile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Gram/culture +ve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Gram/culture -ve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Fungus</td>
</tr>
</tbody>
</table>

### INTERVENTIONS
(Complete this as the procedures are done during the hospital admission)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Date/Time</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCP</td>
<td>/20</td>
<td>□ Failed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ CBD stones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ CBD size:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ES+stone removal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Stenting</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>/20</td>
<td>□ Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Laparoscopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Intraoperative choiandoilogram</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Not done</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ No CBD stones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ CBD stones</td>
</tr>
<tr>
<td>Duct exploration</td>
<td></td>
<td>□ Transcystic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Transductal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Laparoscopic</td>
</tr>
<tr>
<td>Preoperative LFTs</td>
<td></td>
<td>□ Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Abnormal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ BR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ALP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ GGT</td>
</tr>
<tr>
<td>Percutaneous catheter drain</td>
<td>/20</td>
<td>□ Pancreatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Peripancreatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Size of catheter:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Number of times:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Complications:</td>
</tr>
<tr>
<td>Necrosectomy</td>
<td>/20</td>
<td>□ Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Minimally invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Laparoscopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Endoecopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Nephroscopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Number of times:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Complications:</td>
</tr>
<tr>
<td>Laparostomy for ↑ abdo pressure</td>
<td>/20</td>
<td>□ Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Minimally invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Laparoscopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Endoecopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Nephroscopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Number of times:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Complications:</td>
</tr>
<tr>
<td>Other</td>
<td>/20</td>
<td>□ Open</td>
</tr>
</tbody>
</table>

**Doctor’s Name:** ___________________________  **Signature:** ___________________________
Appendix 5. Patient diary used in the EFAP trial

MY ACUTE PANCREATITIS DIARY

Patient Label

Admission date: ___/___/___
Discharge date: ___/___/___
MY ACUTE PANCREATITIS DIARY

What is the diary?
Your acute pancreatitis diary essentially functions as a treatment diary and consists of a number of questions related to your gastrointestinal problem as well as several scales to assess the severity of your symptoms. It is developed for you so that you can see how your condition changed. We hope it can help you to recover from your disease more quickly.

Who has a diary?
All patients with acute pancreatitis who are treated in our hospital have a diary.

Who writes in the diary?
This is your diary. Therefore, only you (or, on your behalf, your relative) may write in the diary.

When can the diary be started?
Diary has to be started on the day after your admission to the hospital. Please fill it in daily until discharge or for the first 10 days in the hospital (whichever comes first), preferably at the same time (e.g. after the evening meal).

Where will the diary be kept?
The diary will be kept next to your bedside.

What happens to the diary when you are discharged?
Once you are discharged from the hospital, please return by mail in the envelope provided. The diary will be confidentially analysed by the Pancreas Network of New Zealand team and securely stored at the Pancreas Network of New Zealand office.

Who can give me more information?
If you would like more information about the diary you can speak to the nurse who is looking after you or ask to speak to Dr. Max Petrov.
DAY 1
(The first day after hospital admission)

1. WHAT HAVE YOU BEEN EATING AND DRINKING?

1. What did you eat or drink over the last 24 hours?

☐ Nothing at all
☐ Liquids only (e.g. apple juice, clear broth, strained or pureed cream soups, gelatin dessert, weak tea)
☐ Enteral tube feed
☐ Soft food, including liquids (e.g. cooked cereals, mashed potato, pureed fruits)
☐ Water only
☐ Solid foods and normal drinking

2. How much did you eat and drink?
Put a cross somewhere along the line below to indicate how much you ate or drank during the last 24 hours. A mark all the way to the left would indicate “Nothing at all”. A mark all the way to the right would indicate “As at times when you are in good health”. Please make only 1 mark.

0 1 2 3 4 5 6 7 8 9 10
Nothing at all As usual

3. How much did you enjoy your eating and drinking?
Put a cross somewhere along the line below to indicate how tasty your feeding was over the last 24 hours. A mark all the way to the left would indicate “Not palatable at all”. A mark all the way to the right would indicate “As palatable as it could be”. Please make only 1 mark.

0 1 2 3 4 5 6 7 8 9 10
Not palatable at all Extremely tasty
II. HOW HAVE YOU BEEN FEELING?

1. During the last 24 hours, have you experienced pain in your abdomen? □ Yes □ No
   If yes, was the pain severe enough to limit your next food intake? □ Yes □ No
   
   Put a cross somewhere along the line below to indicate how intense your abdominal pain was over the last 24 hours. A mark all the way to the left would indicate "No pain". A mark all the way to the right would indicate "Pain as bad as it could be". Please make only 1 mark.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>moderate</td>
<td>worst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Did you receive pain medicine over the last 24 hours? □ Yes □ No
   If yes, did you ask medical staff for this? □ Yes □ No

3. During the last 24 hours, have you experienced nausea? □ Yes □ No
   If yes, was the nausea severe enough to limit your next food intake? □ Yes □ No
   
   Put a cross somewhere along the line below to indicate how intense your nausea was over the last 24 hours. A mark all the way to the left would indicate "No nausea". A mark all the way to the right would indicate "Nausea as bad as it could be". Please make only 1 mark.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>moderate</td>
<td>worst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. During the last 24 hours, have you passed stool? □ Yes □ No
   If yes, have you had loose, very soft or watery stool? □ Yes □ No
   If yes, how many stools did you have over the last 24 hours? □ 1 □ 2 □ 3 □ 4 □ ≥5

5. During the last 24 hours, have you passed flatus? □ Yes □ No
   If yes, was it as usual? □ More than usual □ Usual □ Less than usual
Put a cross somewhere along the line below to indicate how intense your abdominal bloating was over the last 24 hours. A mark all the way to the left would indicate “No bloating”. A mark all the way to the right would indicate “Bloating as bad as it could be”. Please make only 1 mark.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>moderate</td>
<td>worst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. For each symptom mentioned below, please circle the number that best describes how severe the symptom has been during the last 24 hours. Please answer each question as accurately as possible.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (feeling sick to your stomach as if you were going to vomit or throw up)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Retching (heaving as if to vomit, but nothing comes up)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stomach fullness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Bloating (feeling like you need to loosen your clothes)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stomach or belly visibly larger</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Feeling excessively full after feeding (if you had an intake)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

III. MAIN COMPLAINTS

Please identify your 3 main complaints over the last 24 hours, rank them (the complaint ranked first is the most troublesome, the complaint ranked third is the least troublesome among the 3 main complaints), and rate each of the 3 complaints on a 0-10 scale where “0” is “No complaint” and “10” is “Complaint as strong as it could be”.

<table>
<thead>
<tr>
<th>Complaint 1:</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>(specify)</td>
<td>none</td>
<td>moderate</td>
<td>worst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complaint 2:</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>(specify)</td>
<td>none</td>
<td>moderate</td>
<td>worst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complaint 3:</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>(specify)</td>
<td>none</td>
<td>moderate</td>
<td>worst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IV. IMPACT OF SYMPTOMS

These questions are designed to measure how much has your illness and symptoms impacted on you during the last 24 hours. Please circle one number for each question.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I cannot climb a flight of stairs</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I am not able to move easily</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I am not able to stand comfortably for five minutes</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>It is difficult for me to get dressed</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I am unable to care for myself</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I feel dependent on others to care for me</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I am afraid to move because it might cause pain</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I have severe pain in and around my abdomen</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I am not able to move my bowels normally</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I am uncomfortable because I am thirsty</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I do not have a good appetite</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I wake up feeling that sleep has not refreshed me</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I have trouble falling asleep</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I wake up a lot in the night</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I have difficulty concentrating on what I am doing</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I feel helpless</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>I feel anxious</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td></td>
</tr>
</tbody>
</table>

V. CHANGE IN SYMPTOM SEVERITY

Please rate overall change in severity of your symptoms during the last 24 hours using a 15-point scale (-7 to -1 = worse; 0 = no change; and +1 to +7 = better). Please make only 1 mark.

<table>
<thead>
<tr>
<th>Change</th>
<th>-7</th>
<th>-6</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
<th>+4</th>
<th>+5</th>
<th>+6</th>
<th>+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>A very great deal worse</td>
<td>Almost the same, hardly worse at all</td>
<td>Almost the same, hardly worse at all</td>
<td>A very great deal better</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maxim S Petrov - 205 - December 2011
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