MULTIMEDIA ARTICLE – Slide Show

New Approaches for the Treatment of Acute Pancreatitis

Raffaele Pezzilli, Lorenzo Fantini, Antonio Maria Morselli-Labate

Department of Internal Medicine and Gastroenterology, Alma Mater Studiorum - University of Bologna, Sant'Orsola-Malpighi Hospital. Bologna, Italy

Summary

In recent years, a number of articles have been published on the treatment of acute pancreatitis in experimental models and most of them were published about animals with mild disease. However, it is difficult to translate these results into clinical practice. For example, infliximab, a monoclonal TNF antibody, was experimentally tested in rats and it was able to significantly reduce the pathologic score and serum amylase activity, and also alleviate alveolar edema and acute respiratory distress syndrome; no studies are available in clinical human acute pancreatitis. Another substance, such as interleukin 10, was efficacious in decreasing the severity and mortality of lethal pancreatitis in rats, but seems to have no effect on human severe acute pancreatitis. Thus, the main problem in acute pancreatitis, especially in the severe form of the disease, is the difficulty of planning clinical studies capable of giving hard statistically significant answers regarding the benefits of the various proposed therapeutic agents previously tested in experimental settings.

According to the pathophysiology of acute pancreatitis, we may re-evaluate the efficacy of the drugs already available, such as gabexate mesilate, lexipafant and somatostatin which should be probably administered in a different manner. Of course, also in this case, we need large studies to test this hypothesis.

Another great problem is prevention of the infection of pancreatic necrosis. A randomized study has been published to test the hypothesis that probiotics and specific fibres used as supplements in early enteral nutrition may be effective in reducing pancreatic sepsis and the number of surgical interventions. A study named PROPATRIA (Probiotic Prophylaxis in Patients with Predicted Severe Acute Pancreatitis) has been planned to give a more robust confirmation to the previous study. Furthermore, the open question of the prevention of the fungal infection of necrosis is still being debated.

Finally, the prevention of pain relapse after oral feeding in patients with mild or severe acute pancreatitis should be explored. Even if some studies exist on this issue, the question of optimal treatment is still unanswered.

As in other diseases, obtaining results when treating patients with acute pancreatitis is difficult and will take continuous small steps.
Pancreatology held in Lisbon in October 2005.

In the last few years, several new therapeutic options have changed the management of acute pancreatitis; for example, the therapeutic ERCP with endoscopic sphincterotomy in severe biliary pancreatitis, the use of early antibiotic treatment in necrotizing pancreatitis and the demonstration that enteral feeding is able to decrease the inflammatory response. In this paper we describe the therapeutic news which could modify the current approach to acute pancreatitis in the near future. This is possible only because we have new information in order to better understand the pathophysiological processes of the disease.

### Pathophysiology and Clinical Phases of Acute Pancreatitis

<table>
<thead>
<tr>
<th>PHASE</th>
<th>TIMING</th>
<th>INITIAL</th>
<th>EARLY</th>
<th>MIDDLE</th>
<th>LATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st week</td>
<td>2nd week</td>
<td>3rd-4th week</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MAJOR EVENTS</strong></td>
<td><strong>DEATHS</strong></td>
<td><strong>Infectious complications</strong></td>
<td><strong>Acute-phase response</strong></td>
<td><strong>Mechanical obstruction</strong></td>
<td><strong>Other causes</strong></td>
</tr>
<tr>
<td>Acute necrotizing pancreatitis</td>
<td>7</td>
<td>Acute peritonitis</td>
<td>Septic shock</td>
<td>Sepsis</td>
<td>Infection</td>
</tr>
<tr>
<td>Necrotizing pancreatitis</td>
<td>8</td>
<td>32%</td>
<td>12%</td>
<td>19%</td>
<td>37%</td>
</tr>
<tr>
<td>Severe acute pancreatitis</td>
<td>7</td>
<td>26%</td>
<td>0%</td>
<td>6%</td>
<td>12%</td>
</tr>
</tbody>
</table>

We can distinguish three clinical phases regarding the pathophysiology of acute pancreatitis. There is not very much information on the initial phase of the disease in humans and, for the most part, it comes from experimental studies [1]. Of course, it is apparent that we can obtain good therapeutic results only if we treat the pancreatitis as soon as possible.

The time limit for efficacious medical treatment is of no more than 60 hours from the onset of symptoms of acute pancreatitis [2].

Another important aspect as to the correct approach to the management of acute pancreatitis is the correct clinical classification of acute pancreatitis. We should thank Dr. Bradley for his efforts in changing the classification of the disease from a pathological to a clinical point of view [3].

### Severity Classification of Acute Pancreatitis: from the Pathological to the Clinical Point of View

- **Marseille (pathological classification) [4]**
  - Edematous acute pancreatitis
  - Necrotizing acute pancreatitis

- **Atlanta (clinical classification) [3]**
  - Mild acute pancreatitis
  - Severe acute pancreatitis

The work of Bradley can be summarized in the evolution from the Marseille [4] to the Atlanta [3] classification system.
As in other diseases, also in acute pancreatitis, the pathophysiological aspects of the disease should guide our therapeutic approach. On the other hand, we should also consider that the treatment needs to be tailored to each individual patient and we also should take into account the available resources of each Institution.

In the last few years, the need has emerged to treat patients with acute pancreatitis according to new knowledge accumulated from clinical research in order to improve the morbidity and the mortality of the disease.

Since 1994, many papers have been published suggesting the good medical practice to be followed in the treatment of acute pancreatitis [3, 5, 6, 7, 8, 9, 10, 11, 12].

There is no congruence in the various guidelines regarding stratification of severity, diagnosis, treatment and presence of Pancreas Units [13].

In the same way, there are no homogeneous evidence levels in the various guidelines [13].

These differences are quite surprising because...
most of the participants are the same experts who decide on the various guidelines.

In addition to the suggestion of Bradley about the need of guiding the reluctants [13], there is also the need to unify the various guidelines.

One example of rapid evolution of the knowledge of acute pancreatitis is the following: the UK guidelines were released in 1998 [5], revised in 2005 [6] and, after just a few weeks, some researchers asked to change the new 2005 UK guidelines [14].

Another problem with the guidelines is that many clinical practitioners in the same country follow different guidelines [15] and others do not fully apply them in clinical practice [16].

In most of the guidelines, the basic management of acute pancreatitis is not reported: some examples are the control of pain and the control of the nausea, vomiting and ileus.

First of all, what about the control of pain?

There are no extensive studies on the...
pharmacological control of pain in acute pancreatitis [17, 18, 19, 20]; this is quite surprising due to importance of this symptom.

Second, what about the control of nausea, vomiting, and ileus?

### Basic Management of Acute Pancreatitis

#### The Control of Pain

#### The Control of Nausea, Vomiting, Ileus

Naso-gastric suction is often used in patients with acute pancreatitis, even if most of the published studies limit this approach only to the patients with severe disease [21, 22, 23].

### The Naso-Gastric Suction

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients and Study Design</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naccie R</td>
<td>58 patients with mild to moderately severe AP</td>
<td>NG = 37</td>
<td>Most patients with mild or moderately severe acute pancreatitis do not benefit from nasogastric suction</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td>no NG = 31</td>
<td></td>
</tr>
<tr>
<td>Navarrono S</td>
<td>58 unselected patients with acute pancreatitis</td>
<td>NG = 44</td>
<td>Nasogastric suction should be reserved for patients presenting with inflicted pain, a situation which occurred in 1 out of every 8 cases in the present series</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td>no NG = 44</td>
<td></td>
</tr>
<tr>
<td>Sarr MG</td>
<td>60 patients with acute pancreatitis of mild to moderate severity</td>
<td>NG = 29</td>
<td>NG tended to resume and intake later and remain hospitalised longer</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td>no NG = 31</td>
<td></td>
</tr>
</tbody>
</table>

NG = nasogastric suction

Gastric acid secretion inhibition is largely used in patients with acute pancreatitis, even if there are very few studies on this issue and the results are not conclusive [24, 25].

### Gastric Acid Secretion Inhibition

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maiato OE, S</td>
<td>18 pts with acute alcoholic pancreatitis</td>
<td>There was no statistical difference in the course of the illness between the two groups as regards duration of abdominal pain, gastric tenderness, hospital stay or time taken for the patient to resume a normal diet</td>
</tr>
<tr>
<td>56th Mod [24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open study</td>
<td>12 pts did not receive antibiotics</td>
<td></td>
</tr>
<tr>
<td>Moreno–Olmo R</td>
<td>40 controls</td>
<td>*Phenoximine treated patients showed a significant difference in the duration of hyperamylasaemia and duration of pain</td>
</tr>
<tr>
<td>Digestion 1989 [25]</td>
<td>36 pts; 10 mg of phenoximine every 12 h i.v.</td>
<td></td>
</tr>
<tr>
<td>Double blind study</td>
<td>36 pts; 20 mg of phenoximine every 12 h i.v.</td>
<td>*Complications were less frequent and mortality was reduced in phenoximine groups</td>
</tr>
</tbody>
</table>

### Experimental Treatment of Acute Pancreatitis

- More than 2,000 papers on the treatment of acute pancreatitis in experimental models have been published in the last 5 years
- About half of these studies were carried out on endometrial pancreatitis
- Only a few of the substances tested in these studies have been applied in clinical practice

Even if many studies have been carried out, only a few of the substances tested have been applied in clinical practice.

### Infliximab in Acute Pancreatitis

- Infliximab, a monoclonal TNF antibody, was tested in 100 rats randomly assigned to 10 groups
- In acute endometrial pancreatitis and in severe necrotising pancreatitis, the drug significantly decreased serum amylase activity and the histopathological score
- In severe necrotising pancreatitis, it accelerated both parenchymal and fatty tissue necrosis of the pancreas
- It also alleviated alveolar edema and ARDS-like pulmonary complications, but this difference was not significant

This is the first experimental study exploring the usefulness of Infliximab in the treatment of severe acute pancreatitis [26].

### Resveratrol in Acute Pancreatitis

- To evaluate the protective and antioxidative effect of resveratrol, a stilbene derivative, in acute pancreatitis induced by tert-butyl hydroperoxide injection
- Changes in pancreata were much less pronounced in the rats which received resveratrol for 8 days prior to tert-butyl hydroperoxide injection
- In this way it seems that stilbene derivatives may prevent pancreatic cells from undergoing structural changes during acute pancreatitis experimentally induced in rats

Antioxidant treatment for acute pancreatitis is...
a neverending story; this is one of the most recent studies exploring the usefulness of a new antioxidative drug in experimental acute pancreatitis [27].

A paper published in 2001 highlighted the limitations of experimental models in acute pancreatitis [28].

Interleukin-10 represents a case of limitation of experimental research. In fact, this molecule was unable to prevent new organ failures in clinical practice [29, 30].

Polyunsaturated Fatty Acids in Acute Pancreatitis

On the other hand, polyunsaturated fatty acids were able to decrease the length of hospitalization and the duration of jejunal feeding in humans, even if they were not able to decrease the number of new complications [31, 32].

What are the problems in carrying out studies on therapeutic agents in acute pancreatitis?

Designing Future Clinical Trials in Acute Pancreatitis

- The Leipsig Group -

- The high incidence of organ failure within 72 hours after the onset of symptoms has undermined the primary hypothesis, and
power calculations for future studies on severe acute pancreatitis will need to allow for this. Lexipafant had no effect on new organ failure during treatment. This study - performed with an adequately sized sample - has shown that antagonism of the PAF activity on its own is not sufficient to ameliorate SIRS in severe acute pancreatitis: However, if we look at the data reported, we cannot exclude that Lexipafant may have some effect, especially in patients treated within 48 hours from the onset of symptoms [34].

Lexipafant: Critical Appraisal of the Clinical Trials

The trials with infliximab are an example of the "magic bullet" approach which has typified anticytokine trials.

The restoration of homeostasis with a single intervention belies the complex and coordinated nature of the inflammatory response. In clinical practice there is necessity of not using "magic" drugs alone: there is the need for more drugs capable of involving the different aspects of the disease [35].

We also need to change the way results of drug trials are communicated to the medical world [35].

The Need for Clinical Research

Scientific method: clinical trials should be preceded by experimental and pilot studies in order to confirm the safety and the correct dosage and to estimate the necessary efficacy of future trials.

Communication of the results: Communication of the results from the clinical trials in acute pancreatic diseases should be improved. Editors share the responsibility of publishing well-designed and conducted clinical studies whether or not the results are negative.

Commercial influence: The risks associated with dealing with biotechnology companies are well-known. Companies can be under severe pressure to repay the venture capitalists and shareholders. Thus, there is the need for independent monitoring of data and safety in company-sponsored clinical trials.

Treatment of Acute Pancreatitis with Protease Inhibitors

Ten articles of randomized controlled trials evaluating the effects of protease inhibitors (Apoptinin and Gelcatin) for acute pancreatitis were retrieved by systematically searching Medline, Cochrane Library and Ovid databases published from January 1966 through December 2003.

The main outcome of interest was the overall mortality rate from acute pancreatitis.

When protease inhibitors were given to patients with mild pancreatitis, they were not significant (pooled RD 0.06, 95% CI from -0.04 to 0.05).

When protease inhibitors were given to patients with severe pancreatitis, the mortality rate decreased significantly (pooled RD - 0.07, 95% CI from -0.13 to 0.01).

One example may be the highly debated efficacy of protease inhibitors in human acute pancreatitis [37].

A Critical Appraisal of the Clinical Trials in Acute Pancreatitis

Several steps may have to be blocked at the same time and this may be achieved by using combinations of several drugs at the same time or by the multiple actions of a single drug.

Furthermore, we must be aware of several autoimmune phenomena in patients treated with cytokine and anticytokine therapies [36].

Several steps may have to be blocked at the same time and this might be achieved by using several drug combinations at the same...

Furthermore...

time or by the multiple action of a single drug in order to block the protease cascade as well as the cytokine cascade [2].

Another important aspect for the treatment of acute pancreatitis is the prevention of the infection of pancreatic necrosis.

Enteral Feeding and Severe Acute Pancreatitis

- 34 severe acute pancreatitis patients
- SIRS, sepsis, organ failure, and ICU stay were globally improved in the enteral-fed patients
- The acute phase response and disease severity scores (CRP, APACHE II) were significantly improved following enteral nutrition without any change in the CT scan scores
- Enteral feeding modulates the inflammatory and sepsis response in acute pancreatitis and is clinically beneficial

This is the first clinical study demonstrating the beneficial effect of enteral nutrition in decreasing the inflammatory and sepsis response in severe pancreatitis [38].

Early Naso-Gastric vs. Naso-Jejunal Feeding in Severe Acute Pancreatitis

- A total of 59 consecutive patients with objectively graded severe acute pancreatitis were randomized to receive either NG or NJ feeding via a fine bore feeding tube
- A total of 27 patients were randomized to NG feeding and 22 to NJ
- Clinical differences between the two groups were not significant
- Overall mortality was 34.5% with five deaths in the NG group (18.5%) and seven in the NJ group (31.8%)
- The simpler, cheaper, and more easily used NG feeding is as good as NJ feeding in patients with objectively graded severe acute pancreatitis. This appears to be a useful and practical therapeutic approach to enteral feeding in the early management of patients with severe acute pancreatitis

There is no doubt that it is better to administer enteral feeding via a naso-gastric tube than via a naso-jejunal tube [39].

Probiotics and Fibre Supplement in Patients with Acute Pancreatitis

- To determine whether lactic acid bacteria such as Lactobacillus Plantarum 299 could prevent colonisation of the gut by potential pathogens and thus reduce the endotoxins associated with acute pancreatitis

<table>
<thead>
<tr>
<th>Controls (n=22)</th>
<th>Lactobacillus (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (mean±SD)</td>
<td>46.3±13.6</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>17/6</td>
</tr>
<tr>
<td>Etiology (Alcohol:Other)</td>
<td>16/7</td>
</tr>
<tr>
<td>Duration of symptoms (hr) (mean±SD)</td>
<td>24.4±4.1</td>
</tr>
<tr>
<td>Necrotizing pancreatitis</td>
<td>11 (5.8%)</td>
</tr>
<tr>
<td>Severe pancreatitis</td>
<td>15 (65.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive aspiration culture</th>
<th>Controls</th>
<th>Lactobacillus</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive aspiration culture</td>
<td>7/17 (41.2%)</td>
<td>11/17 (64.7%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

There is also no doubt that probiotics associated with enteral feeding may become an alternative therapy replacing early antibiotic use to prevent infection in severe pancreatitis [40].

Probiotic Prophylaxis in Patients with Severe Acute Pancreatitis

- Double-blind, placebo-controlled randomised multicenter trial in which patients will be randomly allocated to a multi-arm probiotic preparation (Biocodex 617) or placebo, it will be performed in 180 hospitals
- The study product is administered twice daily through a nasogastric tube for 28 days or until discharge
- Inclusion criteria: adult patients with a first onset of predicted severe acute pancreatitis with severe trauma 3 or more, CRP 150 mg/L or more, APACHE II score 5 or more
- Exclusion criteria: post-ERCP pancreatitis, multiple trauma, infection/sepsis caused by a mixed disease, nose operation diagnosis of pancreatitis and use of probiotics during the study
- The study product administration starts within 72 hours after onset of abdominal pain
- Primary endpoints: total number of infective complications
- Secondary endpoints: mortality, morbidity, antibiotic resistance, hospital stay and adverse events
- A sample size of 200 patients was calculated to demonstrate that probiotic prophylaxis reduces the proportion of patients with infective complications from 55% in 30%, with odds ratio 0.6 and power 0.8

We are awaiting the results of this study in order to draw the final conclusion on the effectiveness of probiotic prophylaxis in preventing severe complications in severe acute pancreatitis [41].

Antibiotics and Severe Acute Pancreatitis: Pros

Pancreatic infection | ABR: 12% |
Sepsis | ABR: 21% |
Mortality | ABR: 12% |

This meta-analysis shows the need for using early antibiotic therapy in order to prevent...
The authors concluded that all patients with acute necrotizing pancreatitis should receive early antibiotic treatment [42].

However, not all researchers agree that severe acute pancreatitis should be treated with early antibiotic administration [43].

Prophylactic Antibiotic Treatment in Patients with Predicted Severe Pancreatitis: A Frank Discussion

- The pancreatic necrosis was confirmed by CT criteria in only 58 patients
- 5 patients had Staphylococcus epidermidis colonization negative strains and the detection of this species might be considered more a contamination than a true infection
- Once the presence of infected necrosis was determined, it was not clear if surgical intervention was immediate or if it was delayed by the open administration of antibiotics
- 28% of antibiotics-treated patients and 46% of the patients of the placebo group had received an open treatment
- These data could suggest not only the need, but the inevitability, in everyday clinical practice, of performing early antibiotic treatment in the management of severe necrotizing pancreatitis, either prophylactically or "as demand".

Suggested Caloric and Fat Content During the First Five Days of Refeeding

<table>
<thead>
<tr>
<th>Day</th>
<th>Caloric content (kcal)</th>
<th>Lipids (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>1,000</td>
<td>5-10</td>
</tr>
<tr>
<td>3</td>
<td>1,500</td>
<td>15-20</td>
</tr>
<tr>
<td>4</td>
<td>1,600</td>
<td>25-30</td>
</tr>
<tr>
<td>5</td>
<td>1,700</td>
<td>35-40</td>
</tr>
</tbody>
</table>

This is the suggested caloric intake for the refeeding of acute pancreatitis patients [46].

Lanreotide after Oral Refeeding in Patients with Necrotizing Acute Pancreatitis (Study Design)

- To assess the frequency of pain relapse in patients with acute necrotizing pancreatitis after treatment with oral intramuscular injection of lanreotide 30 mg on the day before refeeding
- The refeeding procedure was standardized and progressive
- 23 patients: 11 alcoholics, 7 biliary, 5 other causes
- 12 and 3 or more Isenmann’s criteria
- A: Balthazar score of "D" or "E"
- Median duration of pain and of interruption of oral feeding were 11 days (range 3-21) and 16 days (range 5-34), respectively
- Median hospital stay was 22 days (range 9-41)

To prevent an acute relapse of acute...
pancreatitis, the use of lanreotide has been suggested [47].

In this French study, only 4.3% of the patients treated with Lanreotide had relapse of pain from acute pancreatitis, but 65.2% experienced adverse effect using the drug [47].

There are very few studies evaluating the exocrine pancreatic function after an acute episode of pancreatitis [48, 49, 50, 51].

Enzyme supplementation during the refeeding of patients with acute pancreatitis represents an important issue regarding nutritional support. However, there are no studies showing the possible efficacy of enzyme oral supplementation especially in those patients who suffered from acute alcoholic pancreatitis.

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Correspondence
Raffaele Pezzilli
Dipartimento di Medicina Interna
Ospedale Sant'Orsola-Malpighi
Via Massarenti, 9
40138 Bologna
Italy
References


