

MULTIMEDIA ARTICLE – Slide Show

New Approaches for the Treatment of Acute Pancreatitis

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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

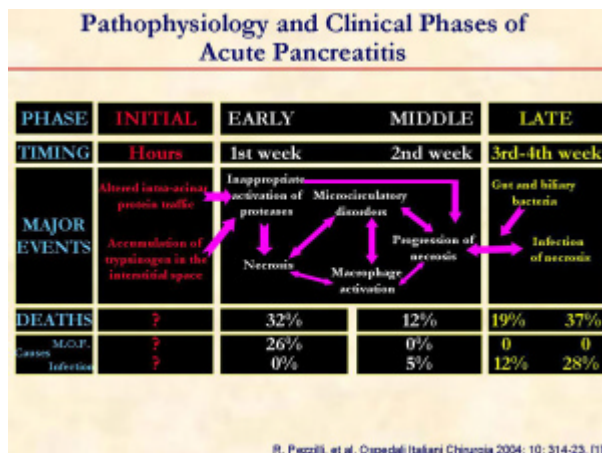
randomized study has been published to test the hypothesis that probiotics and specific fibres used as supplements in early enteral nutrition may be effective in reducing pancreatic sepsis and the number of surgical interventions. A study named PROPATRIA (Probiotic Prophylaxis in Patients with Predicted 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.



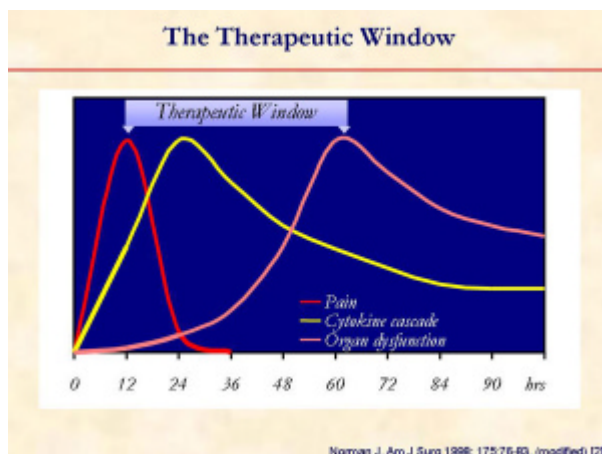
This slide presentation took place at the Meeting of the European Societies of

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.

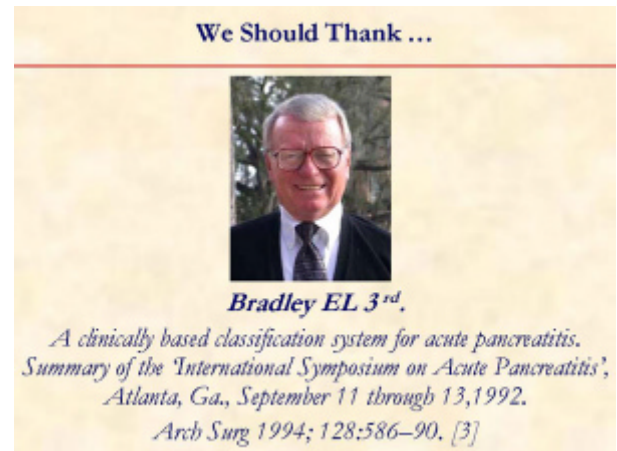


We can distinguish three clinical phases regarding the pathophysiology of acute pancreatitis. There is not very much information on the initial phase of the disease in humans and, for the most part, it comes from experimental studies [1]. Of course, it is apparent that we can obtain good therapeutic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

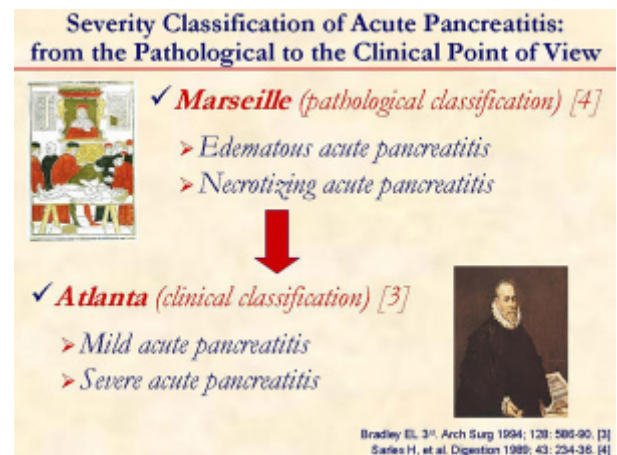


The time limit for efficacious medical

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].



The work of Bradley can be summarized in the evolution from the Marseille [4] to the Atlanta [3] classification system.



Treatment of Acute Pancreatitis



The treatment needs to be tailored to each individual patient, considering the techniques available in each Institution

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.

Practical Guidelines for the Management of Acute Pancreatitis

The practical guidelines represent a new approach for the treatment of acute pancreatitis

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.

Published Papers on Practical Guidelines

- ATLANTA: Bradley EL 3rd. *Arch Surg* 1994; 128:586-90. [3]
- UNITED KINGDOM: *Gut* 1998; 42(Suppl 2):1S-13S. [5]
- *Gut* 2005; 54(Suppl 3):iii1-9. [6]
- SSAT: *J Gastrointest Surg* 1998; 2:487-8. [7]
- SANTORINI: Derrenis C, et al. *Int J Pancreatol* 1999; 25:195-210. [8]
- AISP: Uomo G, et al. *Ir J Gastroenterol Hepatol* 1999; 31:635-42. [9]
- WCG: Tonuli J, et al. *J Gastroenterol Hepatol* 2002; 17(Suppl):S15-39. [10]
- JSAEM: Mayumi T, et al. *J Hepatobiliary Panc Surg* 2002; 9:413-22. [11]
- LAP: Uhl W, et al. *Pancreatology* 2002; 2:565-73. [12]

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].

Congruence of Specific Practical Guidelines

	Atlanta 1994	UK 1998/2005	SSAT 1998	Santorini 1999	AISP 1999	WCG 2002	JSAEM 2002	LAP 2002
Stratification of severity	APACHE II CECT	APACHE II CECT	BMU CECT	N/a	BMU CECT APACHE II APACHE O CECT	CECT X-ray or CECT	APACHE II APACHE II APACHE II	APACHE II
CECT scanning	Severe AP	Severe AP	N/a	Severe AP	Severe AP	Severe AP	Severe AP	N/a
Treatment of pain	N/a	N/a	Yes	N/a	N/a	Yes	Yes	N/a
Treatment of nausea, vomiting, ileus	N/a	N/a	N/a	N/a	Yes	N/a	N/a	N/a
Fluid replacement	N/a	Yes	Yes	N/a	Yes	Yes	Yes	N/a
Early antibiotics	Nonotropy pancreatitis	Nonotropy pancreatitis	Nonotropy pancreatitis	Nonotropy pancreatitis	Nonotropy pancreatitis	Nonotropy pancreatitis	Nonotropy pancreatitis	Nonotropy pancreatitis
ERCP+ES	Cholangitis Jaundice	Severe AP Cholangitis Jaundice	Cholangitis	Severe AP Cholangitis Jaundice	Severe AP Cholangitis Jaundice	Severe AP Cholangitis Jaundice	Severe AP Cholangitis Jaundice	Cholangitis Jaundice
Surgery for sterile necrosis	Rarely	N/a	N/a	Rarely	Rarely	Rarely	Rarely	Rarely
FNA to identify infected pancreatic necrosis	Yes	Yes	N/a	Yes	Yes	Yes	Yes	Yes
Enteral nutrition	N/a	Yes	N/a	Yes	N/a	Yes	Yes	Yes
Efficacy of antiproteases	N/a	No	N/a	No	Severe AP	No	Yes	N/a
Pancreas Units	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/a

AP: acute pancreatitis; N/a: not available Bradley EL 3rd. *Pancreatology* 2003; 3:139-43. (modified) [13]

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

Evidence Level in the Various Practical Guidelines

	Atlanta 1994	UK 1998/2005	SSAT 1998	Santorini 1999	AISP 1999	WCG 2002	JSAEM 2002	LAP 2002
Stratification of severity	B	B	N/a	B	B	N/a	A	N/a
CECT scanning	B	B	N/a	A	A	N/a	B	N/a
Treatment of pain	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
Treatment of nausea, vomiting, ileus	N/a	N/a	N/a	N/a	C	N/a	N/a	N/a
Fluid replacement	N/a	B	B	C	C	C	N/a	N/a
Early antibiotics	N/a	B	B	A	A	B	B	A
ERCP+ES	N/a	A	B	B	A	B	B	N/a
Timing of cholecystectomy	N/a	B	N/a	N/a	B	B	N/a	B
Surgery for sterile necrosis	N/a	B	N/a	A	B	B	B	B
FNA to identify infected pancreatic necrosis	N/a	B	N/a	B	A	N/a	A	B
Enteral nutrition	N/a	A	N/a	B	N/a	A	B	B
Efficacy of antiproteases	N/a	A	N/a	A	A	A	A	N/a
Pancreas Units	B	B	B	C	B	N/a	B	N/a

A: Randomized controlled trial; B: non-randomized clinical studies; C: expert opinion; N/a: not available Bradley EL 3rd. *Pancreatology* 2003; 3:139-43. (modified) [13]

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

The Participants of the Santorini Consensus Meeting




These differences are quite surprising because

most of the participants are the same experts who decide on the various guidelines.

What Do We Ask of Practical Guidelines?

Guiding the Reluctant [13]
but we need to
Address the Guideline Writers' Efforts
in order to
Unify the Guidelines



Bradley EL 3rd. Pancreatology 2003; 3:130-43. [13]

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

Revision of the UK Practical Guidelines

United Kingdom guidelines for the management of acute pancreatitis. Gut 1998; 42 (Suppl 2):i15-i15 [5]

United Kingdom guidelines for the management of acute pancreatitis. Gut 2005; 54(Suppl 3):iii1-9 [6]

Gurusamy KS, Farook M, Tweedie JH. UK guidelines for management of acute pancreatitis: is it time to change? Gut 2005; 54:1344-5. [14]

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].

European Gastroenterologists' Awareness of Practical Guidelines

<i>German Consensus Conference 2000</i>	92%
<i>Atlanta Symposium 1992</i>	53%
<i>World Congress of Gastroenterology 2002</i>	49%
<i>British Society of Gastroenterology 1998</i>	40%
<i>International Association of Pancreatology 2002</i>	31%
<i>Santorini Consensus Conference 1999</i>	20%
<i>Society for Surgery of the Alimentary Tract 1998</i>	14%
<i>Japanese Society of Abdominal Emergency Medicine 2002</i>	6%

Larkisch PG, et al Pancreatology 2005; 5:591-3. [15]

Guidelines for the management of gallstone acute pancreatitis are not being met, resulting in high rates of readmission with related disease

Bergan K, Kingnorth AN. JOP. J Pancreas (Online) 2001; 2:317-22. [16]

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].

Basic Management of Acute Pancreatitis

- *The Control of Pain*
- *The Control of Nausea, Vomiting, Ileus*

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.

Basic Management of Acute Pancreatitis

- *The Control of Pain*
- *The Control of Nausea, Vomiting, Ileus*

First of all, what about the control of pain?

Pharmacological Control of the Pain

Study	Patients with acute pancreatitis	Analgesics	Results
<i>Eisbeley N, Sand J Gastroenterol 1985 [17]</i> Double-blind, placebo-controlled	30	➤ Indomethacin suppositories, 50 mg twice daily	Indomethacin better than placebo
<i>Jakobi R, Sand J Gastroenterol 2000 [18]</i> Double-blind, controlled	49	➤ Euphorphine constant i.v. infusion ➤ Procaine constant i.v. infusion	Euphorphine better than procaine
<i>Stevens M, Appl Nurs Res 2002 [19]</i> Double-blind, controlled	32	➤ Pentanyl/TTS ➤ Demersol i.m.	No statistically significant difference
<i>Kohl S, Digestion 2004 [20]</i> Open, controlled	107	➤ Procaine continuous i.v. infusion ➤ Pentazocine every 6 h (i.v. bolus)	Pentazocine better than procaine

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.

Basic Management of Acute Pancreatitis

- The Control of Pain
- The Control of Nausea, Vomiting, Ileus

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

The Naso-Gastric Suction

Study	Patients and Study Design	Patients	Results
Nacjic R Br Med J 1978 [21] Randomized	58 patients with mild to moderately severe AP	NG = 27 no NG = 31	Most patients with mild to moderately severe acute pancreatitis do not benefit from nasogastric suction
Navarro S Digestion 1984 [22] Randomized	88 unselected patients with acute pancreatitis	NG = 44 no NG = 44	Nasogastric suction should be reserved for patients presenting with intestinal ileus, a situation which occurred in 1 out of every 8 cases in the present series
Sarr MG Surgery 1986 [23] Randomized	60 patients with acute pancreatitis of mild to moderate severity	NG = 29 no NG = 31	NG tended to resume oral intake later and remain hospitalized longer

NG: naso-gastric suction

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].

Gastric Acid Secretion Inhibition

Study	Patients	Results
Maisto OE , S Afr Med J 1983 [24] Open study	➤ 18 pts with acute alcoholic pancreatitis ➤ 15 pts did not receive antacid therapy	There was no statistical difference in the course of the illness between the two groups as regards duration of abdominal pain, epigastric tenderness, hospital stay or time taken for the patient to resume a normal diet
Moreno-Otero R , Digestion 1989 [25] Double blind study	➤ 40 controls ➤ 36 pts: 10 mg of pirenzepine every 12 h i.v. ➤ 39 pts: 20 mg of pirenzepine every 12 h i.v.	• Pirenzepine-treated patients showed a significant difference in the duration of hyperamylasemia and duration of pain • Complications were less frequent and mortality was reduced in pirenzepine groups

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].

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 a half of these studies were carried out on edematous pancreatitis
- Only a few of the substances tested in these studies have been applied in clinical practice

MEDLINE Search, August 2005

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 edematous pancreatitis and in severe necrotizing pancreatitis, the drug significantly decreased serum amylase activity and the histopathologic score
- In severe necrotizing pancreatitis, it ameliorated 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

Oruc N, et al. Pancreas 2004; 28:E1-6. [26]

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

Lawinski M, et al. Pancreas 2005; 31:43-7. [27]

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].

Limitations of Experimental Models for the Treatment of Acute Pancreatitis



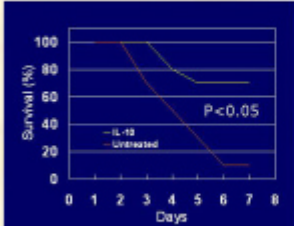
The utility of such experimental models might have limitation, and a full extrapolation of experimental data from laboratory animals to humans must be done with caution

Pastor CM, Frossard J. FASEB J 2001; 15:890-7. [28]

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

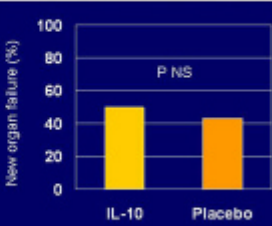
Interleukin-10 in Acute Pancreatitis

Efficacy in experimental study



Zou WS, et al. J Surg Res 2002; 103:121-6. (modified) [29]

No effect in humans

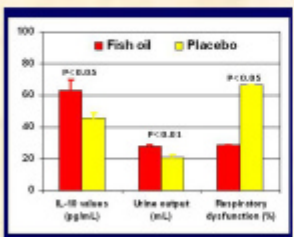


Vitoria A, et al. Pancreatology 2003; 3:496. [30]

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].

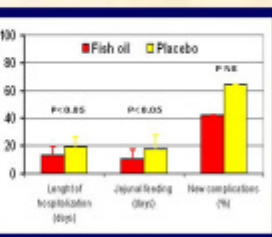
Polyunsaturated Fatty Acids in Acute Pancreatitis

Efficacy in experimental study ...



Foltz T, et al. JPEN 2002; 26:351-6. [31]

... and in humans



Lazebny N, et al. Clin Nutr 2005; 24:198-205. [32]

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].

Problems in Performing Studies on Therapeutic Agents

- *In the last 5 years, only 11 studies have been published on the treatment of human severe acute pancreatitis (most of them on the early antibiotic treatment)*
- *It is difficult to plan clinical studies on acute pancreatitis capable of giving specific answers regarding the benefits of the various proposed therapeutic agents in human clinically severe acute pancreatitis*
- *Furthermore, there is no translational research in the field of acute pancreatitis*

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

Designing Future Clinical Trials in Acute Pancreatitis

- *Therapeutic trials need to record the time from onset of symptoms to intervention*
- *There is the need of using widely accepted prognostic indices to categorize the severity of acute pancreatitis*
- *There is the need for relevant and interpretable end-points:*
 - ✓ *Mortality is important but more work is necessary in developing patient outcomes*
 - ✓ *Good alternatives include the measurement of permanent target organ damage, disability, quality of life, pain scores, category of intervention, surgery, in-patient stay and return to work*
 - ✓ *There is the need of including patients with a single etiology of acute pancreatitis, or at least only patients with a predominant etiology of the disease in the specific country*

Mason J, Srinwardena AK. Pancreatology 2005; 5:113-5. [33]

There is the need to better design future clinical trials in acute pancreatitis [33].

Immune-Manipulation in Acute Pancreatitis - The Lexipafant Example -

The study included 290 patients:

- *151 in the Lexipafant group and 139 in the placebo group*
- *4 patients were subsequently excluded (three due to incorrect diagnosis and one false to a major violation of the protocol)*
- *The analysis of complications regarded 138 patients of the Placebo group and 148 of the Lexipafant group*
- *The analysis of attributable mortality was carried out in 147 patients of the Lexipafant group and in 136 of the Placebo group*
- *The analysis of treatment performed within 48 hours from the onset of symptoms of acute pancreatitis was performed in 104 patients of the Lexipafant group and in 95 patients of the Placebo group*

Complications	Lexipafant	Placebo	Significance
Organ failure	85/148 (57%)	80/138 (58%)	N/S
Systemic sepsis	4/148 (3%)	13/138 (9%)	P=0.023
Pseudocyst	8/148 (5%)	19/138 (14%)	P=0.025
Attributable deaths (pts treated ≤48 hrs)	8/104 (8%)	17/95 (18%)	P=0.034


Johnson CD, et al. Gut 2001; 48:624. [34]

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
- > Deleterious effects have been recorded when single proinflammatory mediators of the inflammatory response were blocked



Abu-Zidan FM, Windsor JA, Eur J Surg 2002; 168:215-9. [35]

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].

Adverse Events of Immune-Manipulation

... we must be aware of several autoimmune phenomena in patients treated with cytokine and anticytokine therapies

Infliximab & Etanercept	<ul style="list-style-type: none"> > Development of anti-DNA antibodies > Development of antinuclear antibodies > Development of anticanalysin antibodies > Systemic lupus erythematosus > Neurological signs and symptoms associated with demyelinating lesions of the CNS
Interleukin 2	<ul style="list-style-type: none"> > Development of antithyroid antibodies > Thyroid dysfunction > Arthritis > Myositis > Systemic sclerosis > Pemphigus vulgaris > Vitiligo > Carpal tunnel syndrome

Furthermore ... Pezzilli R, et al. JOP. J Pancreas (Online) 2004; 5:15-21. [36]

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

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 pancreatitis 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

Abu-Zidan FM, Windsor JA, Eur J Surg 2002; 168:215-9. [35]

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

Treatment of Acute Pancreatitis with Protease Inhibitors

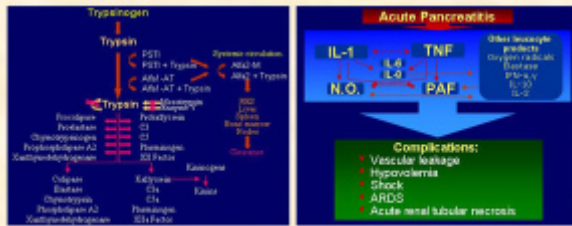
- > Ten articles of randomized controlled trials evaluating the effects of protease inhibitors (Aprotinin and Gabexate) for acute pancreatitis were retrieved by systematically searching Medline, Cochrane Library and Ovid databases published from January 1966 through December 2003.
- > The main outcome 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 0.00; 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)

Sela T, et al. Eur J Gastroenterol Hepatol 2004; 16:1287-93. [37]

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

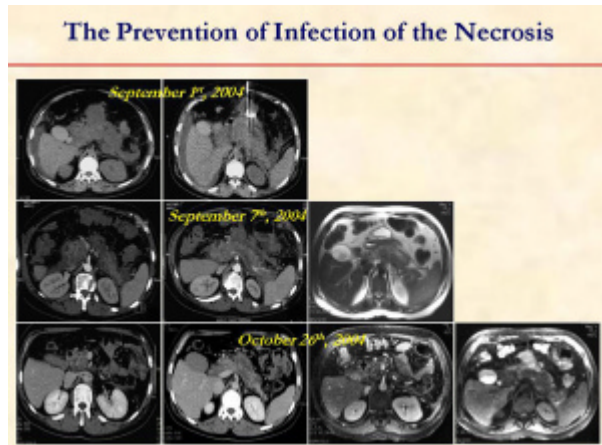
- > Several steps may have to be blocked at the same time and this may be achieved by using combinations of several drugs at the same time or by the multiple actions of a single drug



Norman J. Am J Surg 1998; 175:76-83. (modified) [2]

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

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 enterally-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

Windsor AC. Gut 1998; 42:431-5. [38]

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 50 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 24.5% 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

NG, naso-gastric; NJ, naso-jejunal. Etzock FC, et al. Am J Gastroenterol 2005; 100:432-9. [39]

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 colonization of the gut by potential pathogens and thus reduce the endotoxaemia associated with acute pancreatitis

	Controls (n=23)	Lactobacillus (n=22)
Age (yrs) (mean±SD)	46.5±13.6	44.1±11.1
Sex ratio (M:F)	17:6	16:6
Etiology (Alcohol: Other)	16:7	13:9
Duration of symptoms (hrs) (mean±SD)	21.4±14.1	26.1±13.3
Necrotizing pancreatitis	11 (47.8%)	9 (40.9%)
Severe pancreatitis	15 (65.2%)	17 (77.3%)

	Controls	Lactobacillus	P value
Positive aspiration culture	7/23 (30.4%)	1/22 (4.5%)	<0.05
Septic complications requiring operation	7/23 (30.4%)	1/22 (4.5%)	<0.05

Olsh A, et al. Br J Surg 2002; 89:1103-7. [40]

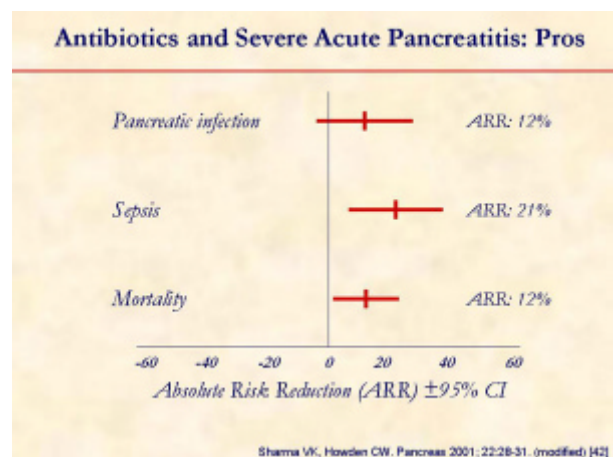
There is also no doubt that probiotics associated with enteral feeding may become an alternative therapy replacing early antibiotic use to prevent infection in severe pancreatitis [40].

Probiotic Prophylaxis in Patients with Severe Acute Pancreatitis

- Double-blind, placebo-controlled randomised multicenter trial in which patients will be randomly allocated to a multispore probiotic preparation (Ecologe 641) or placebo; it will be performed in 15 Dutch 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 (Ivix criteria 3 or more, CRP 150 mg/L or more, APACHE II score 8 or more)
- Exclusion criteria: post-ERCP pancreatitis, malignancy, infection/sepsis caused by a second disease, intra-operative diagnosis of pancreatitis and use of probiotics during the study
- The study-product administration starts within 72 hours after onset of abdominal pain
- Primary endpoint: total number of infectious complications
- Secondary endpoints: mortality, neurotoxicity, 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 infectious complications from 50% to 30%, with alpha 0.05 and power 80%

Besselink MG, et al. BMC Surg 2004; 4:12. [41]

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



This meta-analysis shows the need for using early antibiotic therapy in order to prevent

sepsis and mortality in severe acute pancreatitis [42].

Antibiotics and Severe Acute Pancreatitis: Pros

- Antibiotic prophylaxis significantly reduced sepsis by 21.1% and mortality by 12.3% compared with no prophylaxis
- There was also a non-significant trend toward a decrease in local pancreatic infections
- Antibiotic prophylaxis decreases sepsis and mortality in patients with acute necrotizing pancreatitis
- All patients with acute necrotizing pancreatitis should receive prophylaxis with an antibiotic of proven efficacy

Sharma VK, Howden CW. Pancreas 2001; 22:28-31. [42]

The authors concluded that all patients with acute necrotizing pancreatitis should receive early antibiotic treatment [42].

Antibiotics and Severe Acute Pancreatitis: Cons

- Ciprofloxacin (Cipr 400mg x 2/day) + Metronidazole (Met 500mg x 2/day) (AB) vs. Placebo (P)
- Switch to "Open" treatment infection, sepsis and MOP
- 114 pts with CRP >150mg/L and/or necrosis at CT (58 with AB and 56 with P)

Microbiological Findings in Infected Necrosis		
	Cip/Met (AB)	Placebo (P)
✓ Staphylococcus epidermidis	2	3
✓ E. coli	1	1
✓ Staphylococcus aureus	1	1
✓ Escherichia coli	3	3
✓ Enterobacter	1	0
✓ Lactobacillus spp.	0	1
✓ Candida albicans	1	0
✓ Candida glabrata/tropicalis	0	1

- 12% of AB patients developed infected necrosis vs. 9% in P (P=0.585) (expected 40% vs. 20%)
- 5% mortality rate in AB patients vs. 7% in P (P NS)
- In 76 patients with necrotizing pancreatitis, no differences (also in pts with necrosis >30%)
- Cross-over rate: 28% of the AB patients require a switch to open treatment vs. 46% of P patients (P<0.05)

Isenmann R, et al. Gastroenterology 2004; 126:997-1004. [43]

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 coagulase 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 this was preceded by the open administration of antibiotics
- 28% of antibiotic-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 prescribing early antibiotic treatment in the management of severe necrotizing pancreatitis, either prophylactically or "on demand"

Bassi C, Falconi M. Gastroenterology 2004; 127:1015-6. [44]

- Why did the authors choose antibiotics such as fluoroquinolones which, in a previous clinical study, did not demonstrate efficacy similar to imipenem?
- How many patients were fed enterally?

Pezzi R. JOP. J Pancreas (Online) 2004; 5:161-4. [45]

After the publication of the paper of Isenmann

R, et al. [43], a discussion on its validity was opened [44, 45].

What Are the Criteria for Predicting the Pain During Refeeding in Acute Pancreatitis?

Logistic Score to Predict the Risk of Pain Relapse

=

0.64 a + 1.11 b + 2.18 c - 9.06

- a = Balthazar's CT score (5 classes)
- b = Duration of painful period (5 classes)
- c = Serum lipase concentration on the day before refeeding <3x cN (2 classes)
- 9.06 = Constant

Levy P, et al. Gut 1997; 40:262-8. [46]

Refeeding is crucial in patients who have recovered from an acute episode of pancreatitis but there are very few studies on this issue [46].

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

Day	Caloric content (kcal)	Lipids (g)
1	250	<5
2	1,000	5-10
3	1,500	15-20
4	1,600	25-30
5	1,700	35-40

Levy P, et al. Gut 1997; 40:262-8. [46]

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

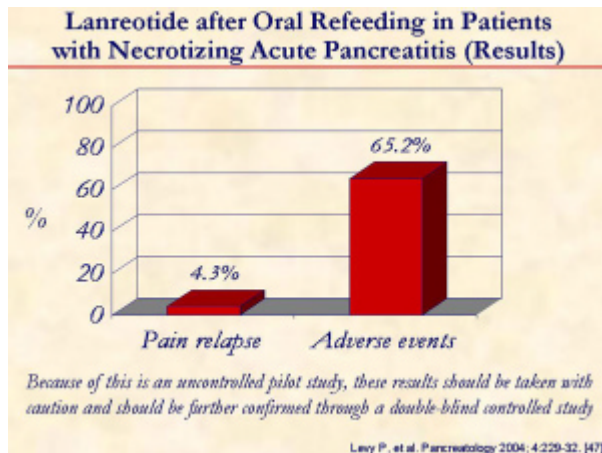
Lanreotide after Oral Refeeding in Patients with Necrotizing Acute Pancreatitis (Study Design)

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

Levy P, et al. Pancreatology 2004; 4:229-32. [47]

To prevent an acute relapse of acute

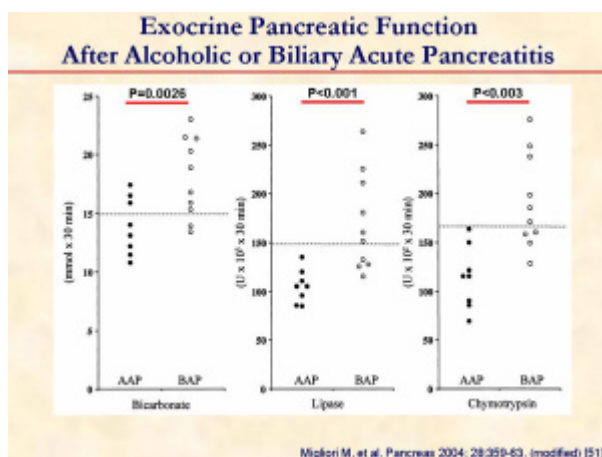
pancreatitis, the use of lanreotide has been suggested [47].



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].

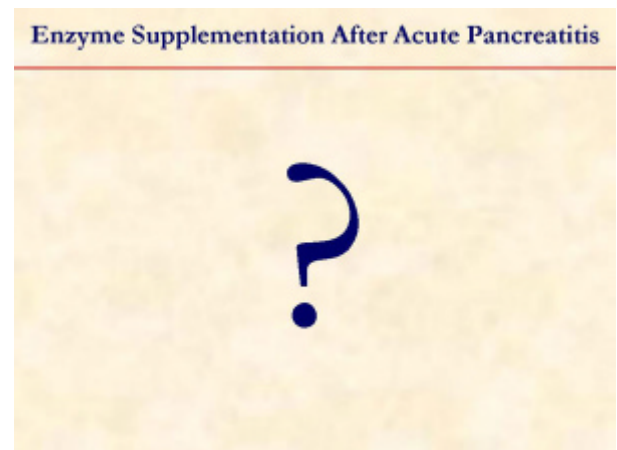
- Studies on Exocrine Pancreatic Function After an Acute Attack of Pancreatitis**
- Ibars EP, et al. *World J Surg* 2002; 26:479-86. [48]
 - Pareja E, et al. *Pancreatology* 2002; 2:478-83. [49]
 - Sabater L, et al. *Pancreas* 2004; 28:65-8. [50]
 - Migliori M, et al. *Pancreas* 2004; 28:359-63. [51]

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



An example of the exocrine pancreatic study

comes from the paper of Migliori *et al.* [51]. In this study patients with acute pancreatitis were studied using the secretin-erulein test. After acute alcoholic pancreatitis, pancreatic insufficiency was significantly more frequent and more severe than after biliary pancreatitis. These findings, together with the fact that the insufficiency was also more persistent, suggest that acute alcoholic pancreatitis may occur in a pancreas which already has chronic lesions.



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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