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CLINICAL PRACTICE GUIDELINES

Pharmacological approach to acute pancreatitis

Ulrich Christian Bang, Synne Semb, Camilla Nøjgaard, Flemming Bendtsen

Ulrich Christian Bang, Synne Semb, Camilla Nøjgaard, Flemming Bendtsen, Department of Gastroenterology, Hvidovre Hospital, Hvidovre DK-2650, Denmark
Flemming Bendtsen, Faculty of Health Sciences, University of Copenhagen, Blegdamsvej 3B, København N DK-2200, Denmark
Author contributions: Bang UC and Bendtsen F wrote the manuscript; Semb S and Nøjgaard C revised the manuscript.
Correspondence to: Ulrich Bang, Department of Gastroenterology, Hvidovre Hospital, Kettegaard Allé 30, Hvidovre DK-2650, Denmark. ulrich_bang@dadlnet.dk
Telephone: +45-26748942 Fax: +45-36473311
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Peer reviewer: Minoti V Apte, Associate Professor, Pancreatic Research Group, South Western Sydney Clinical School, The University of New South Wales, Liverpool, NSW 2170, Australia

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Abstract

The aim of the present review is to summarize the current knowledge regarding pharmacological prevention and treatment of acute pancreatitis (AP) based on experimental animal models and clinical trials. Somatostatin (SS) and octreotide inhibit the exocrine production of pancreatic enzymes and may be useful as prophylaxis against Post Endoscopic retrograde cholangiopancreatography Pancreatitis (PEP). The protease inhibitor Gabexate mesilate (GM) is used routinely as treatment to AP in some countries, but randomized clinical trials and a meta-analysis do not support this practice. Nitroglycerin (NGL) is a nitrogen oxide (NO) donor, which relaxes the sphincter of Oddi. Studies show conflicting results when applied prior to ERCP and a large multicenter randomized study is warranted. Steroids administered as prophylaxis against PEP has been validated without effect in several randomized trials. The non-steroidal anti-inflammatory drugs (NSAID) indomethacin and diclofenac have in randomized studies showed potential as prophylaxis against PEP. Interleukin 10 (IL-10) is a cytokine with anti-inflammatory properties but two trials testing IL-10 as prophylaxis to PEP have returned conflicting results. Antibodies against tumor necrosis factor-alpha (TNF-α) have a potential as rescue therapy but no clinical trials are currently being conducted. The antibiotics beta-lactams and quinolones reduce mortality when necrosis is present in pancreas and may also reduce incidence of infected necrosis. Evidence based pharmacological treatment of AP is limited and studies on the effect of potent anti-inflammatory drugs are warranted.

Key words: Acute pancreatitis; Diclofenac; Gabexate; Indomethacin; Interleukin-10; Necrotizing pancreatitis; Nitrogen oxides; Octreotide; Protease inhibitors; Somatostatin

INTRODUCTION

Acute pancreatitis (AP) is a localized inflammatory condition, which may extent to other organs. The etiology is usually excessive consumption of alcohol or gallstone disease, but is in some cases iatrogenic following medication or endoscopic retrograde cholangiopancreatography (ERCP).

Only a few reviews summarizing the available pharmacological options for treating AP have been published despite various experimental and clinical testing of potential drugs[1]. The aim of the present review is to validate the current literature covering the pharmacological treatment of AP. The main focus is on human clinical trials but some animal experimental models have been included as well (Table 1). AP after ERCP [post-ERCP pancreatitis (PEP)] can be regarded as a clinical "experimental" model of AP and hence is subject to preventive measures. The studies of potentially prophylactic drugs to PEP are therefore included (Table 2).

PATHOPHYSIOLOGY

The pathobiological processes have primarily been investigated in experimental animal models and it is widely accepted that the acinar cells play a central role in the development of AP. The secretory acinar cells (SAC) contain zymogen precursors and the intra-acinar activation of digestive enzymes is a key event in the pathogenesis of AP. The molecular mechanism by which zymogen in AP fails to leave the SAC is unknown. Studies suggest a loss of the terminal actin web or a displacement of one of the SNARE membrane proteins, which regulate exocytosis[2].

The inflammatory response is partly caused by the release of chemokines from SAC, which is followed by recruitment of helper T lymphocytes and macrophages leading to pancreatic edema and accumulation of neutrophils. The systemic release of cytokines including major pro-inflammatory cytokines causes a systemic

Table 1 Pharmacological treatment of acute pancreatitis: Overview of drugs tested in animal experimental models and clinical trials

Name	Mechanism	Effect in animal models	Result in human trials
Somatostatin	Inhibition of pancreatic secretion	No reduced mortality	No reduced mortality
Octreotid	Inhibition of pancreatic secretion	No effect (divergent results)	No reduced mortality
Gabexate mesilate	Protease inhibitor	Reduced histology score	Maybe reduced mortality
N-acetyl-cysteine	Reduction of oxidative stress	Reduced severity	No reduced mortality
Nitrogen oxide	Improvement of micro-circulation	Reduced edema	No published trials
Steroids	Non-specific anti-inflammatory	Reduced mortality	No published trials
Interleukin-10	Anti-inflammatory	Reduced mortality	No published trials
TNF-alpha antibody	Specific anti-inflammatory	Reduced mortality	No published trials
PAF inhibitor	Specific anti-inflammatory	No reduced mortality	No reduced mortality
Antibiotics	Antibacterial	-	Reduced mortality
Probiotics	Prevention of colonization of the gut	-	No reduced mortality

Table 2 Pharmacological prevention of PEP: Overview of drugs tested in clinical trials

Name	Mechanism	Incidence of PEP
Somatostatin	Inhibition of pancreatic secretion	No effect
Octreotid	Inhibition of pancreatic secretion	Probably reduced
Gabexate mesilate	Protease inhibitor	No effect
N-acetylcysteine	Reduction of oxidative stress	No effect
Nitrogen oxide	Improvement of micro-circulation	No effect
Steroids	Non-specific anti-inflammatory	No effect
Interleukin-10	Anti-inflammatory	Probably no effect
TNF-alpha	Specific anti-inflammatory	No published trials
Antibiotics	Antibacterial	Reduced

response, which may include remote organs[3]. The inflammatory process is followed by interstitial edema and the disease will in 10%-15% of the cases progress to necrosis in parts of the pancreas and possible bacterial infection. During an attack of AP the microvascular circulation is affected, which compromises oxygenation of the tissue[2].

The clinical manifestations of AP include upper abdominal pain and symptoms related to the systemic inflammatory response. In complicated cases with involvement of remote organ systems mortality is increased to 5% with ranges from 0% to 47% depending on the severity of the disease. The current treatment of AP is mainly supportive care using analgesics and relevant measures when other organs are involved. Enteral nutrition must be initiated as soon as possible and whenever patients are unable to eat, feeding tubes should be used. Supplementary treatment often involves antibiotics when an infection is suspected and surgery or endoscopic ultrasonic (EUS)-guided drainage in case of infected necrotizing pancreatitis[4].

AP after ERCP is a common complication and reported incidences vary from 5% to 15% in larger series. The majority of the cases are mild self-limiting conditions but up to 1% may develop a severe and potentially fatal pancreatitis. Although the pathophysiological mechanism remains to be elucidated several risk factors are identified: known sphincter Oddi dysfunction, sphincterotomy, injection of contrast more than one time and experience of the endoscopists[5-7].

METHODS

Published trials were identified on PubMed using the MeSH term "AP" in combination with the following MeSH terms: steroids, cortisone, hydrocortisone, corticosteroids, nitroglycerin (NGL), non-steroidal anti-inflammatory drugs (NSAID), celecoxib, COX-Ⅱ, diclofenac, indomethacin, interleukin 10 (IL-10), tumor necrosis factor-alpha (TNF-α), infliximab, Remicade®, etanercept, adalimumab, Humira®, platelet activating-factor (PAF), lexipafant, antibiotics, somatostatin (SS), octreotide, Sandostatin®, probiotics, gabexate, nutrition. Only articles in English were included. Earlier published reviews were manually examined for other relevant studies.

SS/octreotide

SS is a peptide hormone mainly produced in the gastrointestinal tract, where it has an inhibitory effect on gastric emptying, intestinal motility and intestinal blood flow. Furthermore, SS strongly inhibits the production of pancreatic enzymes, which has been the basis for using SS or its analogue octreotide as treatment for AP[8].

Both experimental and clinical trials have been conducted with SS and octreotide, but no effect on the course of the disease has hitherto been demonstrated. Most of the clinical trials comprised only few patients and often patients with interstitial pancreatitis were included although this condition is self-limiting and does not require specific therapy[9]. The largest and best conducted study is a German prospective multicenter study with 302 patients from 32 hospitals with moderate to severe AP randomized to either octreotide or placebo. This study revealed no significant differences between the treatment groups with respect to mortality, rate of complications, surgical interventions or length of hospital stay[10].

Several studies have examined SS or octreotide as prophylaxis to PEP. Various regimes have demonstrated a reduced incidence of PEP compared to placebo: SS administered as a bolus immediately after ERCP (4.4% *vs* 13.3%, $P = 0.01$)[11], SS given as a 12-h continuous infusion starting 30 min before ERCP (1.7% *vs* 9.8%, $P < 0.05$)[12] and octreotide in repeated injections starting 24 h prior to ERCP (2% *vs* 8.9%, $P = 0.03$)[13]. It should be noted that these studies have a fairly high incidence of PEP in the placebo groups. Andriulli *et al* have performed two similar

large, double blind, multicenter, placebo-controlled trials using SS. They used a dosage of 750 micrograms SS as an infusion starting 30 min prior to ERCP, ending 2 h (SS = 183, placebo = 199) or 6 h (SS = 351, placebo = 395) after ERCP. The incidences of PEP in the placebo groups were 6.5% and 4.8% respectively and no advantageous effect of SS was observed[14,15].

The reports published during the years 2002 to 2006 have been summarized in a meta-analysis, which concluded that SS or octreotide have no effect as prophylaxis prior to ERCP[16]. However, this meta-analysis did not include the most recent trial from China with 832 patients. In this study, octreotide was administered as a combination of intravenous infusion and subcutaneous injections and the incidence of PEP in the treatment group (n = 414) and the placebo group (n = 418) was 2.42% and 5.26% respectively (P = 0.046)[17].

Octreotide and SS have thus been investigated in several clinical studies and may have an advantageous effect as prophylaxis prior to ERCP. Optimal dosage and cost-effectiveness still need to be elucidated.

Protease inhibitor-Gabexate mesilate (GM)

The intracellular activation of proteases is a mandatory step in the development of AP and the protease inhibitors could theoretically have an effect in the treatment of AP or as prophylaxis prior to ERCP. The first protease inhibitor, Aprotinin, was widely used in the 1960's but randomized trials could not demonstrate any beneficial effect[18,19]. GM is a synthetic protease inhibitor, which improve histology score in animal models of AP[20].

In the 1980's several reports with a varying number of patients with AP (n = 42 to 223) have been published but none showed any advantage of GM[21-26]. Conversely Chen *et al* observed a significant improved survival in a randomized trial including 52 patients with severe AP who received GM (mortality 33% *vs* 8%)[27]. A meta-analysis later concluded that GM may reduce the mortality in patients with moderate to severe pancreatitis, but the authors also noted that poor quality of the included randomized trials limits the power of this meta-analysis[28].

Several papers from Japan report a reduced mortality rate in patients with necrotizing AP receiving GM as continuous regional arterial infusion (CRAI). However this conclusion is based merely on clinical observations and not placebo-controlled randomized trials[29,30].

Looking at the effect on PEP two large studies by Andriulli *et al* with in total 1172 patients did not reveal any beneficial effect of GM. These results are in conflict with an earlier study by Cavallini *et al*, who in a study of 418 patients observed a PEP incidence of 6% in the GM group and 14% in the placebo group (P = 0.009)[31]. However, a recent meta-analysis concludes that GM does not have an advantageous effect as prophylaxis to PEP[32].

The question continues to be a matter of debate and based on their trial with 608 patients, Manes *et al* argue that high-risk patients may benefit from GM. They administered GM either before or after ERCP compared to a saline solution. The incidence of PEP was 9.4% in the placebo group, and significantly lower (P < 0.01) in the GM groups regardless of the time GM was administered (before ERCP 3.9%, after ERCP 3.4%)[33].

The FDA does not approve GM and the use of GM is not recommended in published guidelines concerning the treatment of AP[4,2,34]. However, Japanese national guidelines recommend the use of protease inhibitors either applied intravenously or as CRAI[35] and GM is also approved in Italy where it is also used as prophylaxis against PEP[36].

Antioxidants

Oxidative stress most likely plays a major role in the early development of AP[37] and several experimental animal models show a beneficial effect of anti-oxidative drugs[38-44]. In humans depletion of antioxidants is observed in AP[45,46] correlating to the severity of the disease[47].

Therapy with antioxidants administered intravenously has been investigated in a prospective double-blind placebo controlled randomized trial on patients with predicted severe AP but no effect on mortality could be demonstrated[48]. The prophylactic effect on the incidence of PEP was tested in two randomized prospective randomized trials with 256 and 106 patients, respectively. N-acetylcysteine (NAC) was administered before and after ERCP and both studies concluded that NAC was without any preventive effect[49,50]. Thus, there is no evidence for the use of NAC.

NGL

NGL is a donor of nitrogen oxide (NO), which causes vasodilatation and reduces cardiac preload. The main indication for using NGL is angina pectoris[51].

Experimental animal models have shown reduced pancreatic edema when administering NO as an infusion[52], but until now no clinical randomized trials using NGL in the treatment of AP have been published. As prophylaxis prior to ERCP three prospective randomized trials have evaluated NGL. NO induces periampullary sphincter relaxation and dilation of the micro vascular vessels, which hypothetically improve pancreatic circulation and nutrition[53].

Sudhindran *et al* observed in a study of 186 patients randomized to either NGL 2 mg sublingual 5 min prior to ERCP or placebo, an incidence of PEP in the NGL group of 8% compared to 18% (P < 0.05) in the placebo group[54]. This finding was supported by Moreto *et al* who randomized 144 patients to either NGL as dermal patch or placebo, and found a significant reduction in the incidence of PEP (4% *vs* 16%, P < 0.05)[55]. Both studies have been criticized for having a surprisingly high incidence of PEP in the placebo groups[56]. In a recently published prospective randomized trial of 318 patients the overall incidence of PEP was 7.5% and no significant difference between the NGL group and the placebo group was revealed[57].

NGL has the optimal qualities as a prophylactic agent as it is cheap and easy to administer. However further trials are needed to determine its potential use as prophylaxis against PEP.

Corticosteroids

Corticosteroids are potent unspecific anti-inflammatory

drugs utilized in a variety of inflammatory diseases. Several case reports have suspected steroids of being the etiology to iatrogenic AP but a definitive relationship has not been established[58-60].

In rat models of AP hydrocortisone has reduced mortality and blood cytokine levels[61,62]. No human trials using steroids as treatment of AP have been published and attempts to show a beneficial effect of steroids as prophylaxis against PEP in prospective placebo-controlled trials have so far been disappointing. In 1999 De Palma *et al* randomized 539 patients to either placebo (n = 266) or hydrocortisone 100 mg (n = 273) administered intravenously prior to ERCP. The total incidence of PEP was 5.3% (n = 28) and no significant difference between the two groups could be demonstrated[63]. In a Polish trial published in 2001, 300 patients received oral prednisone 40 mg, allopurinol 200 mg or placebo 15 h and 3 h prior to ERCP. The total incidence of PEP was 10.7% and no significant difference among the three groups was displayed[64]. Sherman *et al* have confirmed these negative findings in an even larger prospective trial with 1115 patients[65].

Although steroids have the potential to inhibit the inflammatory cascade there is no evidence for the use of neither hydrocortisone nor prednisone as prophylaxis against PEP.

NSAID

NSAID have an analgesic as well as an anti-inflammatory effect. Most NSAID act as non-selective inhibitors of the enzyme COX which catalyses the formation of prostaglandins and thromboxane from arachidonic acid. NSAID are used for virtually every known inflammatory disease.

Salicylic acid and indomethacin have in isolated case reports been related to the development of AP[66-68] as has the selective cyclooxygenase (COX)-2 inhibitor celecoxib[69-72].

Experimental animal models studying the effect of NSAID on AP have been contradictory and not revealed any effect on mortality[73-76].

The only randomized human study on the therapeutic effect of NSAID on AP has been conducted by Ebbehøj *et al* who included 30 patients randomized in two groups receiving either indomethacin suppositories 50 mg twice daily for 7 d or placebo. No difference in serum amylase or calcium was observed but patients in the indomethacin group demanded less opiate as analgesics during hospitalization. Mortality was not registered[77].

Two studies testing the prophylactic effect of indomethacin given prior to ERCP to prevent PEP have been published. Montano *et al* included 117 patients, who received either indomethacin suppositories 100 mg or placebo 2 h prior to ERCP. The incidence of PEP was 2.5% and 6.8% respectively but the difference was not significantly different[78]. In a larger study from Iran 490 participants received 100 mg indomethacin suppositories or placebo and an incidence of PEP of 3.2% in the indomethacin group and 6.8% in the placebo group was observed. The difference was only borderline significant different (P = 0.06) and a post hoc analysis showed significant lower incidence of PEP in the subpopulation of patients who underwent pancreatography[79]. However this conclusion was hampered by the fact that the post hoc analysis was conducted on 10 subpopulations, which in general reduces the statistical power considerably[80].

Another NSAID, diclofenac, has been investigated in a study including 220 patients receiving either diclofenac suppositories 100 mg or placebo immediately after ERCP. PEP occurred with lower frequency in the group receiving diclofenac compared to the placebo group (6% *vs* 15%, $P < 0.05$)[81].

The overall impression from placebo-controlled trials suggests a beneficial effect of NSAID used as prophylaxis against PEP. Both diclofenac and indomethacin can be administered easily as suppositories and are inexpensive drugs. Still, placebo controlled randomized trials with a larger sample size are needed to verify this promising effect.

IL-10

IL-10 is produced and released by the helper T cells and its primary effect is anti-inflammatory. Clinical observations have shown increased levels of IL-10 in the blood during AP but its role in the treatment of AP remains to be determined[82,83]. The effect of IL-10 on AP has been validated in two experimental studies which showed a reduced mortality[84,85].

No human study on the therapeutic effect of IL-10 has been conducted but the prophylactic effect of IL-10 on PEP has been evaluated in two randomized studies. No significant difference among the IL-10 and placebo-treated group was observed in a study with 200 patients receiving either recombinant IL-10 (8 μg/kg) or placebo (9% *vs* 11%, P = 0.65)[86]. A second study randomized 137 patients to placebo or IL-10 (4 μg/kg or 20 μg/kg) administered 30 min prior to ERCP. Overall incidence of PEP was 14% and a significant difference in the incidence among the three groups was noted (24%, 10%, and 7%). However the incidence of PEP in the placebo was remarkable high[87].

The results from these two published studies do not definitively support the use of IL-10 as prophylaxis against PEP.

TNF-α

During AP the serum level of TNF-α is elevated[88,89]. The synthesis and release of TNF-α takes place in macrophages located in the pancreas. SAC may as well release TNF-α and do also express TNF-α receptors during AP[90-92]. A possible relationship between genetic polymorphism and severity of AP has been established[93].

Blocking the TNF-α mediated inflammation with anti-TNF-α antibodies or pentoxifylline seems to have a beneficial effect on histology score and mortality in experimental animal models[94-98].

No data on humans has hitherto been published apart from a single case-report concerning a patient with interstitial pancreatitis. In this case, a male patient with severe bloody diarrhea due to segmental Crohn's disease also showed signs of AP. Serum amylase was high and ultrasound and abdominal computer tomography (CT) scans revealed an edematous pancreas. Because of these

findings treatment with steroids and azathioprine was abandoned and instead a single infusion with infliximab 5 mg/kg was administered without complications. The patient's overall condition improved and serum amylase levels normalized[99].

Thus experimental data suggest a potential role of specific TNF-α inhibition in the treatment of AP, but high risk of bacterial infection during AP is a matter of concern. Infliximab has been evaluated in alcoholic hepatitis, another condition associated with a high risk of bacterial infection. The administration of prednisolone 40 mg daily and infliximab 10 mg/kg at wk 0, 2 and 4 showed an increased mortality due to infection and the study was terminated prematurely by the monitoring committee[100].

Hence clinical studies on AP must be carefully designed to evaluate the safety of infliximab or other specific TNF-α inhibitor.

PAF

PAF was discovered in the 1970's and soon recognized to be an important inflammatory mediator[101]. Later studies with experimental pancreatitis revealed that PAF is released during AP[102] and induce AP when infused in arteries supplying the pancreas[103,104]. Experimental studies have shown a benefit from PAF inhibition with various antagonists on pancreatic edema and systemic inflammation as well as a decreased bacterial translocation[105-107].

As a consequence of the promising results with experimental AP different clinical studies have evaluated the effect of PAF inhibition. The first trial consisted of 83 patients with AP receiving lexipafant (n = 42) or placebo (n = 41). Lexipafant was administered intravenously (60 mg/d for 3 d) and follow-up was assessed for 5 d by Organ Failure Score (OFS). The investigators reported a greater reduction in OFS in the lexipafant group (0.905 *vs* 0.341, P = 0.048), but during the 5 d period mortality was unaffected[108]. These findings were confirmed in a second trial including only patients with severe AP. The participants received lexipafant (n = 27), 100 mg/d for 5-7 d or placebo (n = 23). In the treatment group a larger reduction in OFS was registered (1.42 *vs* 0.17, P = 0.003). Overall mortality was 18% with no difference between the groups[109]. The last study was published in 2001 and involved 286 patients with severe AP. Lexipafant (100 mg/d, n = 148) or placebo (n = 138) was administered for 7 d. No positive effect could be shown neither on OFS nor mortality[110]. It has been argued that data on the effect of lexipafant on mortality from experimental AP were warranted before initiation of human trials and the sponsor's communication of the result has been questionable[111]. After the termination of the clinical trials the lack of effect on mortality in experimental AP was acknowledged[112]. Randomized trials on sepsis were also disappointing[113,114] and inhibition of PAF in the treatment of AP has thus been abandoned.

Antibiotics

Antibiotics is used to prevent or treat infected necrosis in the pancreas and does not have potential to change the pathobiologic course of AP. Infected necrosis in pancreas is a major clinical problem during AP which severely deteriorate the prognosis[115,116]. Hence, administration of antibiotics to prevent infection has been evaluated in several randomized trials.

Sainio *et al* randomized 60 patients with necrotizing pancreatitis. The inclusion criteria were C-reactive protein > 120 mg/L and pancreatic necrosis verified by an abdominal CT scan. The treated group received infusion of cefuroxim 1.5 g × 3 daily, while patients allocated to the control group only received antibiotics in case of clinical signs of infection. A significant higher mortality was registered in the control group compared to the cefuroxim group (23% *vs* 3%, P = 0.03)[117].

Pederzoli *et al* randomized 74 patients with CT verified pancreatic necrosis to receive either imipenem or placebo but no effect on mortality was registered[118]. In another prospective randomized study with 90 patients Nordback *et al* administered imipenem intravenously 1.0 g × 3 daily and found a reduced incidence of multiorgan failure compared to the control group (28% *vs* 76%, P = 0.0003) but no difference in mortality[119].

The studies described above are open-label trials. In 2004 Isenmann *et al* published a controlled double-blind study of 114 patients with CT verified necrotizing AP. The inclusion criteria were C-reactive protein > 150 mg/L and/or CT-verified pancreas necrosis. Placebo was compared to a combination of ciprofloxacin and metronidazole and if any complications occurred the treatment was converted to open conventional treatment. No difference in mortality or incidence of pancreas necrosis could be shown[120].

A Cochrane meta-analysis of 294 patients with CT-verified pancreas necrosis showed a reduced mortality in patients with necrotizing AP when beta-lactams and quinolones were administered intravenously as prophylaxis[121].

The subject continues to be a matter of debate and recommendations from major clinical associations have different approaches to this issue[4,2,34].

Studies on the effect of prophylactic antibiotics given prior to ERCP are limited. In a study by Raty *et al* with 315 patients cephtazidime was administered intravenously prior to ERCP compared with a control group. They found reduced incidence of PEP and cholangitis in the treatment group (3% *vs* 9%, P = 0.009)[122]. However the study was not placebo-controlled and routine administration of antibiotics prior to ERCP cannot be recommended until randomized placebo controlled studies confirm this finding.

Probiotics

Intestinal permeability is increased during AP, which may facilitate translocation of bacteria from the intestinal lumen. Oral probiotics are living microorganisms that exert health benefits beyond those of inherent basic nutrition[123].

Olah *et al* conducted two prospective placebo controlled double-blinded studies of the therapeutic effect of probiotics to AP. The studies were published in 2002

and 2007 including 45 and 62 patients with interstitial or severe AP. In the latter study reduced mortality in the probiotics groups was observed but the difference was not statistical significant[124,125].

CONCLUSION

As described in this review we only have limited evidence based pharmacological approaches when treating AP and none of these are curative. Several treatments including animal experimental studies have been tried in order to establish evidence for etiology based medical treatment (Tables 1 and 2). In Italy and Japan gabexate is used routinely with the aim to limit pancreatic auto-digestion, but as reported in this review there is no conclusive evidence for this approach.

Octreotide may be considered as prophylaxis against PEP but high cost of this peptide hormone limits its potential in clinical practice. A much cheaper alternative is NSAID, which may be considered as prophylaxis against PEP.

Antibiotics are the drugs of choice when infection is evident. However, recommendations regarding the prevention of infected pancreatic necrosis are contradictory.

Various problems are encountered when designing clinical studies of AP. The low incidence of severe necrotizing AP constitutes a major problem, which demands multicenter studies. Another clinical challenge is the resemblance of AP to infection and before initialization of any experimental anti-inflammatory therapy bacterial infection must be refuted. This delays the start-up of the experimental protocol and causes bias as the patients in the meantime receive anti-bacterial treatment. A possible solution could be to administer antibiotics to all patients in combination with specific anti-inflammatory treatment or placebo.

In spite of these challenges the search for pharmacological treatment of AP must be sustained. As we present in this review experimental animal models support a potential effect of several anti-inflammatory drugs, which are candidates for randomized trials. The most interesting of these potential drugs is probably steroids, which are standard treatment of numerous inflammatory diseases but have never been investigated in the treatment of AP.

Because the outcome of the disease depends highly on the involvement of other organs, developing methods that inhibit the inflammatory signaling pathways presents a great potential. As new information regarding the inflammatory pathways continues to emerge from animal and clinical trials, specific treatment targeting these inflammatory processes should be considered. It is our opinion that animal models at this time support clinical trials with anti-TNF-α antibodies although a randomized trial must be designed not forgetting the safety issue.

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