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Treatment of Acute Pancreatitis
Focus On Medical Care

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Abstract

Acute pancreatitis has an incidence of about 300 per 1 million individuals per year, of which 10–15% of patients develop the severe form of the disease. Novel management options, which have the potential to improve outcome, include initial proper fluid resuscitation, which maintains microcirculation and thereby potentially decreases ischaemia and reperfusion injury. The traditional treatment concept in acute pancreatitis, fasting and parenteral nutrition, has been challenged and early initiation of enteral feeding in severe pancreatitis and oral intake in mild acute pancreatitis is both feasible and provides some benefits. There are at present no data supporting immunonutritional supplements and probiotics should be avoided in patients with acute pancreatitis. There is also no evidence of any benefits provided by prophylactic antibacterials in patients with predicted severe acute pancreatitis. A variety of specific medical interventions have been investigated

(e.g. intense blood glucose monitoring by insulin) but none has become clinically useful. Lessons can probably be learned from critical care in general, but studies are needed to verify these interventions in acute pancreatitis.

Acute pancreatitis is a common condition with a yearly incidence of about 300 per 1 million individuals reported in the Western world.[1-3] In 10–15%, a severe form of acute pancreatitis develops with a profound systemic inflammatory response, which may potentially escalate to organ dysfunction with an associated mortality of about 15%.[4,5] Improvements in critical care and active initial management, including fluid resuscitation, have tended to decrease mortality,[1,5] although morbidity and mortality, as well as the societal resources used, are still substantial.

Traditional surgical interventions to remove pancreatic necrosis in patients with severe acute pancreatitis have become more selective, now being restricted to patients with infected pancreatic necrosis or the development of an abscess, and non-responding sepsis and organ failure.[5,6] As infected pancreatic necrosis has become the main indication for surgical intervention, this has led to a delay in the surgery as such infections have been reported to develop first after 2–4 weeks.[7] Furthermore, a randomized trial comparing early (within 72 hours of admission) with late (more than 12 days from admission) surgical intervention demonstrated a higher mortality rate in patients who received early intervention.[8] This has also been demonstrated in a retrospective series.[9] For this reason, current guidelines on the management of acute pancreatitis do not recommend necrosectomy within the first 2 weeks after onset of disease, and if possible even later.[6,10,11] The importance of early and definite management of associated gallbladder/gallstone disease has also been emphasized in order to avoid recurrent episodes of pancreatitis. Figure 1 presents an algorithm for the current management of acute pancreatitis.[5,10]

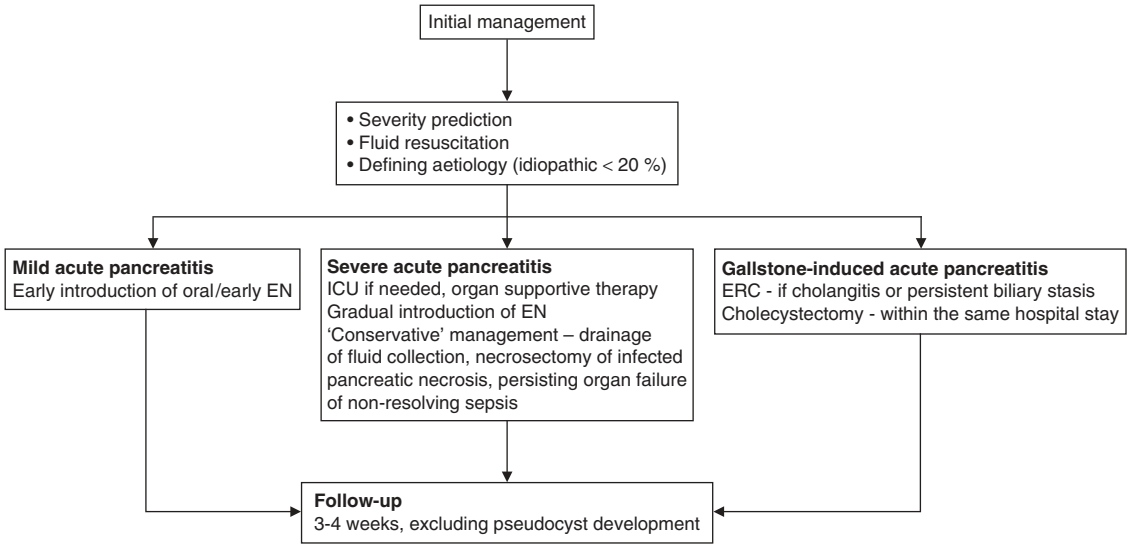

Fig. 1. Algorithm for the management of acute pancreatitis. **EN** = enteral nutrition; **ERC** = endoscopic retrograde cholangiography; **ICU** = intensive care unit.

This review summarizes current indications for different non-surgical therapeutic interventions of potential importance for the course of disease. As a variety of interventions have been tried over the years, we focus on treatments in current use, and on value and evidence. Furthermore, we examine some pathophysiological mechanisms involved in regulating the course of disease as they represent potential future targets of intervention.

1. Fluid Resuscitation

Hypovolaemia (a systolic blood pressure <100 mmHg) at admission has been shown to correlate with an increased mortality in patients with predicted severe acute pancreatitis.[12] Hypovolaemia is the result of the often profound increase in endothelial barrier permeability induced by systemic inflammatory response syndrome (SIRS), correlating with the magnitude of the proinflammatory response. The early initiation of aggressive fluid resuscitation is probably one of the most important factors that have improved outcomes over the years. This minimizes ischaemia and reperfusion injury, which correlate with the concomitant inflammatory response, regulating the course of disease. Sometimes, massive amounts of fluid are needed during the initial resuscitation in order to minimize or at least decrease ischaemia and reperfusion injury.[13] Thus, immediate circulatory resuscitation and thereby restoration of the microcirculation represents one of the most powerful and effective interventions, especially in patients with predicted severe acute pancreatitis.

If uncontrolled, a hyperinflammatory state may progress to organ dysfunction. In patients with severe acute pancreatitis, the magnitude of the proinflammatory response correlates with the severity and concomitant course of disease.[14] A simple predictive tool is C-reactive protein (CRP). A CRP level exceeding 150 mg/L, a cut-off level that has been arbitrarily chosen, within the first 72 hours correlates with the occurrence of necrotizing pancreatitis and the degree of severity.[15,16] Other markers that have been studied are pancreatic lipase, polymorphonuclear elastase, pancreatic amylase and α1-antitrypsin, although none has proven to be a truly successfully marker in predicting the outcome of acute pancreatitis.[15]

2. Organ Dysfunction and Mortality

As a consequence of uncontrolled ischaemia and reperfusion injury, organ dysfunction may develop, which is responsible for early (within the first week after onset) deaths in acute pancreatitis. After the first week, slightly more than half of deaths in pancreatitis occur and are then mostly associated with a combination of multiple organ dysfunction and sepsis.[1,17]

For severity scoring in acute pancreatitis, the Atlanta classification is still predominantly used.[18] However, it has been modified because early transient (resolving within 48 hours) organ failure has not been demonstrated to be associated with any increase in mortality.[19] The most relevant scoring systems for organ dysfunction are, however, the Sepsis-Related Organ Failure Assessment and Marshall scores, allowing the sequential determination of organ failure and correlation with outcome/mortality.[20]

Gut barrier failure has been suggested to aggravate the course of pancreatitis and an increase in permeability has also been noted in patients with pancreatitis. Increased gut permeability is believed to occur early during the course of disease and as a consequence of SIRS.[21,22] The exact importance of this increase in permeability with potential translocation of bacteria and toxins remains to be proven. However, it should be stated that when pancreatic necrosis becomes infected (by gut origin bacteria), mortality increases substantially, representing a highly prognostic factor.[23]

3. Nutrition

Acute pancreatitis is, in its severe form, initially a hyperinflammatory state with a pronounced catabolic state, where the catabolic processes can be aggravated by insufficient nutritional supplementation during the acute phase. This affects both outcome during hospital stay and, not least, the frequently prolonged recovery

seen after severe acute pancreatitis. Traditionally, nutritional management has been in favour of the 'putting the pancreas at rest' concept, i.e. the use of parenteral fluid and nutrition until normalization of laboratory and clinical findings has occurred.

However, an increasing number of studies have indicated positive results from providing patients with early enteral nutrition in gradually increasing amounts. In general, the tube positioning has been distal (nasojejunal) and ordinary enteral nutritional formulas have been used.[24,25] Enteral nutrition provided through a nasogastric tube has even been successful in patients with severe acute pancreatitis.[26] The use of nasogastric early enteral nutrition was found in a recent study to be both feasible and without adverse effects compared with the traditional treatment used in the 'pancreas at rest' concept. This regimen provided better blood glucose control in patients with prognostic severe acute pancreatitis, but had no influence on hospital stay, infectious complications or gut permeability, as has otherwise been previously indicated in some reports.[27] Thus, it may be that early proximal feeding in severe acute pancreatitis provides some benefits but does not solve all problems.

In patients with mild acute pancreatitis, it was shown that patients who were allowed to eat directly decreased their hospital stay by one-third without any noted adverse effects or any increase in recurring pancreatitis compared with traditional initial fluid and nil by mouth.[28]

Therefore, plain enteral nutrition is feasible and provides metabolic and beneficial effects. Early oral intake shortens hospital stay.

4. Supplements to Enteral Nutrition

In patients with severe acute pancreatitis, there are currently not enough data to recommend the addition of immunonutrients. For critical illness in general, though, the administration of parenteral glutamine has been reported to reduce complications and even mortality.[29,30] However, the unselective use of immunonutrition in critically ill patients, especially during the later phases of critical illness, could even be hazardous and increase mortality.[31]

5. Probiotics

The study performed by Olah et al.[32] raised expectations that probiotics might be of benefit in patients with severe acute pancreatitis, by reducing infectious complications and the incidence of infected pancreatic necrosis, and improving overall outcome. However, results of studies have not been consistent and after the recently published Dutch PROPATRIA (Probiotics in Pancreatitis) study, where a probiotic mixture was provided to patients with predicted severe acute pancreatitis, the value of probiotics in acute pancreatitis has been questioned. In the PROPATRIA study, an increase in bowel ischaemia and mortality in the probiotic group was seen compared with patients not receiving probiotics.[33] The authors conclude that ''probiotics can no longer be considered harmless adjuncts to enteral nutrition, especially in critically ill patients or patients at risk for non-occlusive mesenteric ischaemia''. Thus, at present, probiotics cannot be recommended in the management of patients with acute pancreatitis, and should be avoided until additional studies are performed.[34]

6. Prophylactic Antibacterial Treatment

The indications concerning the use of antibacterial prophylaxis in patients with severe acute pancreatitis have gradually changed towards a more selective use. An initial meta-analysis performed on a number of studies using different types of antibacterial prophylaxis, showed an overall positive effect on outcome after prophylactic antibacterial administration.[35,36] Thereafter, an increased risk of fungal infections associated with an increase in mortality was reported.[37] More recent meta-analyses have suggested that only antibacterial prophylaxis using carbapenems are of any proven value,[38] and that prophylactic antibacterials do not prevent infection or pancreatic necrosis or the associated mortality.[39] Furthermore, two double-blind, placebo-controlled trials have failed to

show any significant advantages with the administration of prophylactic antibacterials.[40,41]

Thus, at present, antibacterial prophylaxis cannot be recommended because of a lack of proven effects in patients with predicted severe acute pancreatitis.

7. Specific Medical Treatment in the Management of Acute Pancreatitis

7.1 Somatostatin Analogues and Octreotide

The use of somatostatin and octreotide in acute pancreatitis has been the subject of a number of studies. However, overall, no beneficial effects of the treatment have been reported and thus these agents cannot be recommended in the management of acute pancreatitis.[42-44]

7.2 Antioxidants

Oxygen free radicals most probably play a central role in the pathophysiology of acute pancreatitis, at least during the early stages of the disease. Acute pancreatitis induces the generation and release of reactive oxygen free radicals, including superoxide anions, hydrogen peroxide and hydroxyl free radicals.[45,46] In experimental acute pancreatitis, the use of antioxidants has been found to be partly effective,[47] although no clinical data support the use of scavengers and antioxidants in acute pancreatitis.

7.3 Protease Inhibitors

The presence of activated proteolytic enzymes in acute pancreatitis and the proposed imbalance between proteases and antiproteases have raised the possibility that administration of antiproteolytic agents, including the intracellular trypsin inhibitor gabexate, could be of beneficial value in the management of acute pancreatitis. However, this regimen has not produced beneficial results supporting this theory in clinical studies,[48,49] although occasional reports have been published where gabexate reduced both complications[50] and improved survival.[51]

7.4 Corticosteroids

To date, there are no clinical studies available that support the use of corticosteroids specifically in acute pancreatitis.[52] Experimentally, the use of corticosteroids has been reported to be of some benefit.[53] Corticosteroids have been shown to suppress the inflammatory response in general, probably partly through intracellular inhibition of nuclear factor-κB (NF-κB).[54,55] Low doses of hydrocortisone and fludrocortisone have been reported to reduce the risk of death in patients with septic shock and relative adrenalin insufficiency, and in critically ill patients in general.[56]

7.5 Phospholipase A2 and Nitric Oxide

It has been proposed that the acute lung injury seen in acute pancreatitis is mediated by phospholipase A2 through nitric oxide (NO) production by alveolar macrophages. Pulmonary injury in experimental pancreatitis has been prevented by administration of a phospholipase A2 inhibitor.[57] However, the experimental results are both contradictory and confusing. NO has also been reported to inhibit pancreatitis-induced lung injury, possibly by decreasing pulmonary neutrophil influx.[58] NO has been claimed to both protect against pancreatic injury[59,60] and contribute to the development of acute pancreatitis.[61] Overall, NO seems to exert different actions in different settings depending on the vascular bed and the severity of the disease. These types of interventions are not available for clinical use and because of the variable potency (modulation, e.g. of NO, represents a major challenge) are difficult to regulate.

8. Acute-Phase Response in Acute Pancreatitis

8.1 Nuclear Factor-κB

The proinflammatory response is regulated through the transcription factor NF-κB. Experimental data suggest that NF-κB plays a central role in the development of acute pancreatitis.[62] Blockade of NF-κB activation prior to induction

of experimental pancreatitis has been shown to improve survival[63] and reduce expression of inflammatory cytokines.[64] However, the rapidly initiated systemic response and concomitant tissue injury/organ dysfunction limits the potential clinical application.

8.2 Cytokines

Cytokine release probably represents an important early predictor of severity in acute pancreatitis. The initial peak of tumour necrosis factor-α levels seems to be followed by an increase of interleukin (IL)-6[65,66] and IL-8 levels, and these levels appear to be useful indicators of clinical severity.[67] The presence of the initial proinflammatory response in acute pancreatitis has led to studies on cytokine inhibitor treatment in experimental acute pancreatitis. Pretreatment with an IL-10 agonist diminished acute injury in acute necrotizing pancreatitis.[68] A decrease in the severity of experimental pancreatitis and a reduction in levels of proinf1ammatory cytokines, pancreatic oedema, necrosis and inflammatory cell infiltrates were seen following IL-10 treatment.[69] Furthermore, pretreatment with IL-8 antibodies inhibited cytokine response and acute lung injury in experimental pancreatitis.[70] Administration of IL-1β converting enzyme inhibitor after induction of pancreatitis decreased mortality in severe taurocholate-induced pancreatitis.[71] Clinical support of the application of these treatment strategies has not been reported.

8.3 Adhesion Molecules

Expression of adhesion molecules probably plays a central role in acute pancreatitis, and constitutes a prerequisite for concomitant tissue injury and the further development of organ dysfunction. Neutrophils are sequestered at the site of adhesion molecule expression.[72-74] Treatment with antibodies against, for example, intercellular adhesion molecule-1 (ICAM-l), has been shown to reduce the severity of pancreatitis-associated, gut endothelial barrier dysfunction in rats.[75] ICAM-l antibodies have been reported to decrease both local pancreatic injury and systemic pulmonary injury in experimental pancreatitis.[76]

8.4 Platelet-Activating Factor Antagonists

Platelet-activating factor (PAF) is a proinflammatory lipid mediator shown to play a significant role in acute pancreatitis. Beneficial effects from the PAF antagonist lexipafant in the experimental setting have led to clinical trials.

In 83 patients with acute pancreatitis of mixed severity, treatment with lexipafant for 3 days decreased the incidence of organ failure and the organ failure scores.[77] In 50 patients with predicted severe acute pancreatitis, lexipafant treatment for up to 7 days decreased organ failure scores, and tended to decrease mortality and systemic complications.[78] In 290 patients with an APACHE II score of >6, lexipafant treatment for 7 days, initiated within 72 hours of onset of symptoms, had no effect on the development of new organ failure, but reduced organ failure scores by day 3 and decreased systemic sepsis and pseudocyst formation.[79] This study was followed by a large trial of 290 patients with pancreatitis with an APACHE II score of ≥6 and a history of acute pancreatitis for no more than 48 hours. No difference was found between the two doses of lexipafant tested and placebo.[80]

At present, despite the initial promising results, the use of a PAF antagonist does not seem to improve outcome in patients with acute pancreatitis.

8.5 Granulocyte Colony-Stimulating Factor

Granulocyte colony-stimulating factor has been reported to decrease bacterial translocation[81] and the rate of distant infection in experimental acute pancreatitis.[82]

8.6 Anti-Coagulation and Anti-Inflammatory Approaches

Immediate activation of protein C has been shown in experimental acute pancreatitis.[83] Whenever tissue damage occurs, such as sepsis

or endothelial injury, activated protein C decreases thrombin and fibrin formation, thereby decreasing the risk of thrombosis.[84] Several anti-coagulatory agents have been proven to possess anti-inflammatory properties. Recombinant human activated protein C has been reported to reduce mortality in patients with severe sepsis.[84] The protein C anti-coagulant pathway interferes with both microvascular coagulation and inflammation.[85]

The potential of other anti-coagulant agents for use in patients with sepsis has been suggested by data from experiments with tissue factor pathway inhibitor[86] and an inhibitor of activated factor Xa.[87]

This type of anti-inflammatory approach using anti-coagulants has still not been tried in acute pancreatitis, but could be considered of potential benefit, if the increased risk of bleeding is taken into account. The cross-talk between coagulation and inflammation is most interesting, and warrants further studies as it may represent a future mode of intervention.

Overall, no specific treatment that can be recommended exists in patients with severe acute pancreatitis.

9. Why No Magic Bullets?

Treatment based on intervention against isolated individual pathophysiological observations has generally been without proven value in the management of acute pancreatitis. Evidently, the window of potential therapeutic intervention seems quite limited as a result of the rapid onset of the very complex and interactive mechanisms involved, resulting in an initially predominantly hyperinflammatory response. Thus, treatment strategies directed at blocking various individual, especially proinflammatory, mechanisms have failed. There is a need for both further mapping of the pathophysiological events, and a more tailored and probably multimodal approach to prevention and treatment, given the lack of a common pathway regulating SIRS and the concomitant development of organ dysfunction.

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