Medical treatment of acute pancreatitis

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Acute pancreatitis (AP) is one of the most common diseases in gastroenterology. The incidence of AP per 100,000 people ranges from 10 to 46 cases per year. Two percent of all patients admitted to hospital are diagnosed with AP. During the last decade, an increasing incidence was observed, mostly because of a higher sensitivity of diagnostic tests. With regard to the clinical course of the disease, discrimination between mild edematous disease (75% to 85% of all cases) with mortality below 1% and severe hemorrhagic-necrotizing pancreatitis (15% to 25% of all cases) with a fatal outcome in 10% to 24% is important. Both clinical courses occur regardless of the underlying etiology of the disease. Eighty percent of all cases of AP are linked etiologically to gallstone disease or immoderate alcohol consumption, while pancreatitis caused by hypercalcemia, hyperlipidemia, or infectious agents is rare.

Both courses of the disease (mild and severe) can result in "restitutio ad integrum" or end with various degrees of irreversible destruction of the gland. To allow adequate monitoring and treatment for the disease, it is advised to admit patients to a hospital that also provides an intensive care unit (ICU). The requirement for frequent clinical assessments, laboratory studies, and re-evaluation of organ destruction employing CT or MRI strongly argues against treating these patients on an outpatient basis (Fig. 1).

Prognostic markers for the severity of acute pancreatitis

Prediction of the outcome and course of the disease is desirable at the time when the patient presents in the emergency room; nevertheless it is often difficult. Serum activities of amylase and lipase are not helpful for

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                    ┌─────────────────────────────────────────┐
                    │   Clinically suspected acute pancreatitis │
                    │ (Severe upper abdominal pain, elevated    │
                    │         pancreatic enzymes)               │
                    └─────────────────────────────────────────┘
                                      │
                    ┌─────────────────────────────┐
                    │      Fluid Resuscitation     │
                    │  CVP>8 cm H2O,  Hkt 30-35%   │
                    └─────────────────────────────┘
                                      │
     ┌────────┐     ┌─────────────────────────────┐     ┌──────────────┐
     │ Severe │ ←── │    Assessment of severity    │ ──→ │ Mild/Moderate│
     └────────┘     │ (APACHE II score, Ranson     │     └──────────────┘
         │          │        score, CRP)           │            │
       ┌─────┐      └─────────────────────────────┘     ┌─────────────────────────┐
       │ ICU │                                          │   Medical management    │
       └─────┘                                          │   Early enteral feeding,│
         │                                              │ pain medication, fluid  │
 ┌──────────────────┐                                   │ resuscitation, ERC if   │
 │ Biliary pancreatitis │                               │ gallstone impaction is  │
 │ (ERC within 48 hrs   │                               │      suspected          │
 │ if gallstone         │                               └─────────────────────────┘
 │ impaction is         │                                            │
 │ suspected)           │                               ┌─────────────────────┐
 └──────────────────┘                                   │     Discharge       │
         │                                              │ When pain free and  │
 ┌──────────────────┐                                   │ oral feeding        │
 │ Contrast enhanced CT │                               │ reestablished       │
 └──────────────────┘                                   └─────────────────────┘
         │                                                        │
 ┌────────────────┐        ┌────────────────┐
 │ Necrosis > 30 %│ ←────→ │ Necrosis < 30 %│
 └────────────────┘        └────────────────┘
         │                          │
 ┌────────────────┐                 │
 │   Antibiotics  │                 │
 │ (for up to     │                 │
 │  4 weeks)      │                 │
 └────────────────┘                 │
         │                          │
 ┌──────────────────────────────────────────────────────────────────┐
 │ Enteral nutrition, Pain treatment, Treatment of organ failure when │
 │                           needed                                   │
 └──────────────────────────────────────────────────────────────────┘
         │                                          │
 ┌───────────────┐                          ┌───────────────┐
 │ No Improvement│                          │  Improvement  │
 └───────────────┘                          └───────────────┘
         │                                          │
 ┌────────────────────┐                     ┌─────────────────────┐
 │ CT/US - guided FNA │                     │     Discharge       │
 └────────────────────┘                     │ When pain free and  │
         │                                  │ oral feeding        │
 ┌──────────────┐     ┌────────────────┐    │ reestablished       │
 │Infected      │ ←─→ │ Sterile        │    └─────────────────────┘
 │necrosis      │     │ necrosis       │
 └──────────────┘     └────────────────┘
         │                    │
 ┌────────────────────┐       │    ┌─────────────────────────┐
 │ Necrosectomy and   │       ├──→ │    Elective surgery     │
 │ lavage             │       │    │ When extent of necrosis │
 │ (Minimally invasive│       │    │ precludes recovery      │
 │ if feasable)       │       │    └─────────────────────────┘
 └────────────────────┘       │
                              │    ┌─────────────────────────┐
                              └──→ │ Continued conservative  │
                                   │ management              │
                                   │ (When extent of necrosis│
                                   │ permits complete        │
                                   │ recovery)               │
                                   └─────────────────────────┘
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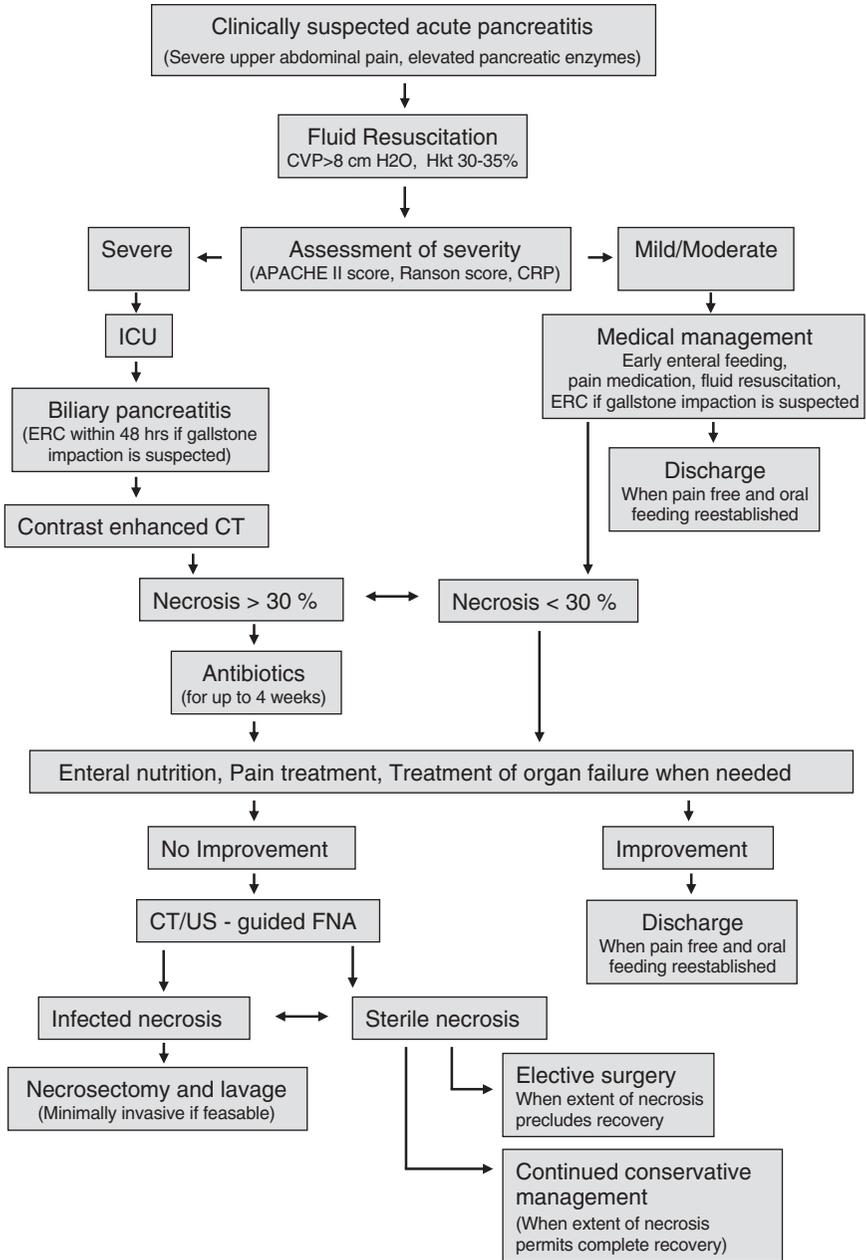
Fig. 1. Algorithm for the medical management of acute pancreatitis (AP). In a case of suspected pancreatitis for the above-mentioned signs, the authors would suggest to follow the above outline flow chart for the diagnosis and treatment of AP.

determining disease severity. Because AP is a mild disease in 80% of patients without associated mortality, it is important to identify the 20% of patients who are likely to develop severe disease associated with major complications and who benefit from early intensive care monitoring. Besides an initial clinical assessment by an experienced gastroenterologist or surgeon, there are several prognostic and diagnostic markers and scoring systems that help in distinguishing severe from mild disease.

If a patient presents with three or more signs for organ failure according to the Ranson or Imrie score, or if he or she develops extrapancreatic complication (eg, respiratory or renal insufficiency), or if pancreatic necrosis is diagnosed on contrast-enhanced CT scan, the course of the disease will in all likelihood be severe [1].

Dynamic contrast-enhanced CT (DCT) is the imaging modality of choice for staging the disease and for the detection of complications of AP [2]. DCT has been shown to provide a diagnostic sensitivity of 87% and an overall detection rate of 90% for pancreatic gland necrosis. DCT has two major roles in evaluating patients with known or suspected AP: initial staging of the disease severity, and early detection of complications. The morphologic severity of AP can be defined using the CT severity index developed by Balthazar et al (Box 1). Comparison of the CT severity index (CTSI) with mortality indicates a good correlation between higher values on CTSI and morbidity and mortality (Table 1). CTSI is derived as follows: first the severity of the acute inflammatory process is categorized into stage A through E, corresponding to scores of 0 to 4, respectively. Definitions for stage A through E are given in Box 1. Second, the presence, extent, or absence of gland necrosis is assessed. If necrosis is present, the extent is estimated as less than one third of the tissue, one half, or greater than one-half on the basis of the area of the parenchyma involved on axial scans. A score of 0 is given if no necrosis is present, and scores of 2, 4, and 6 for less than one third, up to one half, and greater than one half, respectively. Thus AP can be scored with up to 10 points (see Table 1). The question remains

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Box 1. CT grading system of Balthazar [1]

Grade A, normal pancreas consistent with mild pancreatitis
Grade B, focal or diffuse enlargement of the gland, including contour irregularities and inhomogeneous attenuation but without peripancreatic inflammation
Grade C, abnormalities seen in grade B plus peripancreatic inflammation
Grade D, grade C plus associated single fluid collection
Grade E, grade C plus two or more peripancreatic fluid collections or gas in the pancreas or retroperitoneum

Table 1
CT severity index [1]

Index	Morbidity	Mortality
0–3	8%	3%
4–6	35%	6%
7–10	92%	17%

whether a CT scan should be performed during the first 2 days of admission when parenchymal damage may not have reached its maximal extent. If extensive necrosis is established, patients should be transferred to an ICU or high-dependency unit and treated with antibiotics.

As a stand-alone prognostic marker, elevated CRP levels (C-reactive protein) of greater than 130 mg/L implicate a complicated course of the disease, with a sensitivity of 85% in the first 72 hours after the onset of symptoms, although other causes of an acute phase response such as cholangitis or pneumonia need to be ruled out first [3]. Leukocyte immigration and activation also may determine local and systemic complications of AP. This has been demonstrated by using leukocytes scintigraphy, which revealed that an initial positive scan was associated with a later severe or lethal course of the disease [4]. It is therefore not surprising that the quantification of circulating levels of granulocyte elastase as a leukocyte marker (polymorphonuclear leukocyte [PMN]-elastase) alone has been shown to be a reliable method for predicting severity of the disease. The sensitivity and specificity of this test are above 90%. Although a positive predictive value of almost 80% was calculated at the time of admission, a positive predictive value of 98% was calculated 24 hours after admission if the cutoff is set at 200 μg/L. The negative predictive value is 98% at admission for PMN-elastase [5].

In an attempt to use the activation of pancreatic zymogens to determine the severity of the disease, trypsinogen activation peptide (TAP) has been evaluated. Urinary TAP concentration has been shown to correlate with the severity of AP at admission, but its measurement by a manual enzyme immunoassay with limited stability restricts its use as an emergency room test [6]. Employing a similar priniciple, a Finnish group developed a dipstick test for urinary trypsinogen 2. They were able to show a higher positive-likelihood ratio for the urinary trypsinogen-2 test strip than for CRP at 24 hours after admission. To evaluate this method further, multi-center trials need to be conducted [7]. The implications of hematocrit as a prognostic marker for the severity of AP are based on recently published studies that remain controversial. A hematocrit of more than 44% or the absence a fall in hematocrit during the first 24 hours after admission and fluid resuscitation predicts pancreatic necrosis with a positive predictive value of 96% and multi-organ failure with a positive predictive value (PPV) of 97% [8]. A retrospective data analysis from Lüneburg (Germany) failed to demonstrate a correlation between hematocrit and the clinical course, but a hematocrit in the normal

range predicted the absence of pancreatic necrosis with a high negative predictive value [9]. Elevated hematocrit levels result from hemoconcentration because of the loss of large amounts of fluid into the retroperitoneal and peritoneal cavity [9]. Hemoconcentration as indicated by high hematocrit needs to be treated aggressively with fluid substitution.

Another marker that has been evaluated as a prognostic indicator for pancreatitis is procalcitonin. Alternative splicing of procalcitonin leads to the production of calcitonin-related peptide, which directly induces peripheral vasodilatation with extravasation of fluid. As a direct consequence, hypovolemia occurs. This is related to multi-organ failure. Elevated calcitonin-related peptide expression is induced by a fall in serum calcium concentrations or bacterial infection. It remains a matter of discussion whether high procalcitonin levels should be regarded as valuable diagnostic and prognostic marker for the prediction of infected necrosis in pancreatitis or for a severe course of the disease. This question is being investigated in a large multi-center European trial. Nevertheless the data are insufficient for a final assessment of this marker [10,11]. There is no conclusive evidence for a role of proinflammatory cytokines (eg, interleukin [IL]-6, IL-8, IL-18, and IL-2-receptor) as clinical markers for severe AP.

If doubts remain whether the course of the disease will be mild or severe, patients should be kept under close monitoring for early detection and treatment of complications.

Enteral nutrition versus total parenteral nutrition

In the past, patients with AP received nothing by mouth, because it was believed that any stimulation of the exocrine pancreas by fluid or solid nutrients would affect the disease course negatively. Now it is known that the pancreas already is at rest during pancreatitis, and restoring secretion would be a much more physiological strategy than resting the organ. Increasing evidence suggests that enteral feeding is safe and may reduce complications by maintaining the intestinal barrier function and by preventing and reducing bacterial translocation from the gut. Furthermore, enteral nutrition eliminates some complications of parenteral nutrition, such as catheter sepsis (2% even if the catheter is managed appropriately) and less common complications such as arterial laceration, pneumothorax, thrombosis, thrombophlebitis, and catheter embolism. In more than eight prospective randomized clinical trials [12–19], evidence emerged that enteral nutrition is most likely superior to parenteral nutrition in outcome. Additionally, the cost of enteral nutrition is only 15% of the cost of total parenteral nutrition. This and the fact that enteral nutrition is clearly not harmful in pancreatitis make it an increasingly accepted treatment modality [20]. In some cases, it is not possible to meet the required calorie intake by means of enteral nutrition alone to prevent catabolism. In these cases, enteral nutrition should be given to some extent by means of a nasogastric

or nasojejunal feeding tube to prevent atrophy of the intestinal mucosa and loss of barrier function. In addition, the required calories should be supplemented parenterally. There is some evidence that enrichment of intravenous nutrition with glutamine could reduce leaky bowel syndrome [21,22] but experience in pancreatitis remains limited. As for the systemic inflammatory response, Imrie et al found a reduced rate of pulmonary complications in patients treated with enteral nutrition compared with the group on parenteral nutrition, and Gupta et al found decreased CRP levels in patients with enteral nutrition [23].

Nasogastric tube or orally feeding

To treat paralytic ileus, the placement of a nasogastric tube is indicated. In contrast, continuous suction of gastric juice to prevent stimulation of the pancreas is obsolete [24–27]. As most patients find nasogastric suction very uncomfortable, only those with ileus should be treated in this manner. In a randomized controlled trial, the Glasgow group compared enteral nutrition by means of a nasojejunal tube with nutrition by means of a nasogastric tube. No disadvantages were found for nutrition by means of a nasogastric tube. Taking into account the frequent rate of dislocations of nasojejunal tubes and the required endoscopic replacements, nasogastric enteral feeding seems to be the more feasible option in daily clinical practice.

The decision when to begin oral feeding and with what diet to begin oral feeding arises for most patients during recovery from AP, because feeding may cause a relapse of pain and recurrence of the disease. Some help in this decision may be derived from studies in healthy people. The rate of pancreatic enzyme secretion directly correlates to the nutrient composition of a meal and to the rate of caloric delivery to the duodenum. The secretion of pancreatic enzymes decreases when more carbohydrates are ingested, particularly when the carbohydrate content surpasses 50% of the total caloric intake [28]. In AP, the risk of recurrent pain is 21% whenever oral feeding is started. Half of the pain relapses occur on the first or second day of oral feeding, with a greater risk if the patient recovers from necrotizing pancreatitis. It is essential to start oral feeding with a diet that is readily digestible, and food intake can be started at the earliest time point in a pain-free patient. The value of special pancreas diets is rather questionable and not supported by clinical studies. Patients mostly dislike them, because they are rather taste-free. There are also regional and cultural differences in the approach of re-feeding (eg, in France prolonged abstinence from food was never regarded as an adequate treatment option in AP unless severe cases of the disease were treated, whereas prolonged fasting was considered de rigueur for German patients even with mild pancreatitis). The value of not only enteral but also early oral feeding is much more evident today, even in Germany.

Prevention of ulcers and gastritis in pancreatitis patients

Patients suffering from severe AP under intensive care treatment or on mechanical ventilation are prone to develop peptic ulcers or erosive gastritis. Therefore, in most cases it is indicated to use prophylaxis for peptic ulcer disease. Histamin$_2$-antagonists are the therapeutic agents of choice for this purpose, while antacids do not seem to have the same efficiency, and proton pump inhibitors officially are not listed for ulcer prevention in most countries, although they are more effective acid suppressants. For patients who are not on mechanical ventilation and who take oral food, a prophylactic treatment for ulcer disease is not indicated. On the other hand, in patients with adult respiratory distress syndrome (ARDS) and on mechanical ventilation, the risk of gastric bacterial overgrowth in a basic milieu and subsequent aspiration pneumonia needs to be balanced against the risk from ulcer complications. Although the risk from ulcer bleeding versus aspiration pneumonia from gastric bacterial growth has been studied (and determined to be in favor of using H2-Blockers), no such studies exist for the prophylactic use of proton pump inhibitors.

Fluid resuscitation and rehydration

Maintaining an adequate intravascular volume is probably the most essential therapeutic goal in the treatment of AP. If missed, it is also the most consequential mistake. Patients with AP can sequester enormous amounts of fluid, not only into the retroperitoneal space and the intraperitoneal cavity (pancreatic ascites), but also into the gut and the pleural cavity. Adequate fluid resuscitation may require 5 to 10 L of either crystalline or colloidal fluids in 24 hours during the first days after admission. Experimentally, hemodilution to a hematocrit of around 30% with dextran-60 improves pancreatic microcirculation and oxygenation. There are no data available on whether colloids or crystalline solutions are superior for rehydration in people and whether colloids improve pancreatic microcirculation and disease outcome. Clinical practice suggests a ratio of 1:3 for colloids and crystals. To estimate the required fluid substitution, central venous pressure should be monitored closely together with hourly urine excretion and daily hematocrit measurements. Central venous pressure should be raised to approximately 8 to 12 cm of water. Adequate fluid substitution can be assumed when the hematocrit falls to between 30% and 35%. Low urinary output in patients with severe AP most frequently indicates prerenal cause and should be monitored closely, as it may indicate persistent volume depletion that can advance to renal failure from acute tubular necrosis. In this setting, aggressive fluid replacement may cause peripheral and pulmonary edema without improving urinary output. Inadequate volume substitution results in vasoconstriction of splanchnic vessels followed by reduced microcirculation in the pancreas. This, again, may propagate additional tissue necrosis.

Treatment of pain

As a consequence of the activation of pancreatic proteases and tissue necrosis inflammatory mediators, are released locally. These mediators not only facilitate an inflammatory process but also can have a direct effect on sensory fibers of the celiac plexus (T5-T9) and therefore mediate visceral pain. Patients with AP often suffer from great visceral pain. Adequate pain relief is therefore one of the most important and urgent treatment goals. There are several concepts to pain relief that need to be evaluated carefully on an individual basis. In general, the combination of nonsteroidal analgesia with a centrally active drug should be considered. In German-speaking countries, the systemic administration of intravenous procaine hydrochloride has long been a popular alternative to opiates but has been demonstrated to be completely ineffective for the treatment of pain in patients with pancreatitis [29,30]. Concerns that morphine analogs may affect the course of pancreatitis negatively because of their effect on the sphincter of Oddi are also unwarranted [31]. Some authors prefer meperidine over other opiates in pancreatitis but this alleged advantage has not been studied in controlled trials. Tramadol, as an alternative to other opiates, should not be considered in patients with AP, because nausea and vomiting are much too common adverse effects in this group of patients according to the authors' personal experience.

Some centers recently have begun to use thoracic epidural analgesia to treat pain in AP. This not only leads to fast pain relief but also decreases the need for opiates and therefore is associated with less systemic adverse effects. Moreover, epidural analgesia can prevent the development of subileus or ileus. Although effective, the application of epidural analgesia requires considerable technical skills, and not all patients qualify (eg, those with impaired hemostasis or those on sedatives) [32,33].

The role of antibiotics in treatment of acute pancreatitis

Because the development of infected pancreatic necrosis significantly increases the mortality in patients with AP, much attention has been given to the prevention and early identification of patients at risk of developing gram-negative pancreatic sepsis. The major source of gram-negative bacteria is the gut, and one concept of preventing infected necrosis is to decontaminate the intestine selectively with nonabsorbable antibiotics. In one prospective controlled clinical trial on selective decontamination, the rate of pancreatic infections was reduced in patients who received neomycin. Gram-negative intestinal colonization was associated with a 3.7-fold increased mortality [34].

During the last two decades, the use of systemic antibiotics in the treatment of pancreatitis has been discussed intensively, and concepts have changed regularly. The predominant bacterial strains found in pancreatic

tissue or blood cultures from pancreatitis patients are *Escherichia coli, Klebsiella, Staphylococcus,* and *Pseudomonas.* Recent studies have shown that prophylactic antibiotic treatment in mild disease has no beneficial effect, but leads to a selection of bacterial strains resistant to antibiotics. Because infected pancreatic necrosis is associated with a 70% to 80% mortality, patients with proven pancreatic necrosis might profit from prophylactic antibiotics. Several studies have addressed this issue, and the prevailing opinion suggests that:

- Between 25% and 72% of pancreatic necroses become infected.
- Infection of pancreatic necrosis most frequently is found between week 2 and 4 from the disease onset.
- Certain antibiotics such as clindamycin, imipenem, meropenem, metronidazole, fluoroquinolones, and cephalosporins reach the pancreatic tissue sufficiently well, whereas aminoglycosides do not.
- Early antibiotic treatment of patients with pancreatic necrosis may have a significant beneficial effect on outcome and even mortality [35–39].

The results of subsequent trials that have addressed the same issue have not yet been reported and may change the final assessment of the benefits of antibiotic treatment for pancreatitis.

In recent years, it became evident that frequent and unreflected use of broad-spectrum antibiotics leads to an increased rate of secondary fungal infections [40]. In 20% of resection specimens from patients with necrotizing pancreatitis, fungal infection was detected with synchronous evidence for fungi in blood culture from these patients [41]. Many of these patients suffered from fungal sepsis, which was not treated adequately. Randomized studies to evaluate the antimycotic treatment of choice for this condition and whether prophylactic treatment can prevent fungal infection and reduce mortality are not available. Prophylactic fluconazole treatment was shown to reduce *Candida* infections in a retrospective study but failed to affect mortality [42]. Tissue penetrance into the pancreas also has not been assessed for many antifungal drugs.

Endoscopic sphincterotomy

Alcohol abuse and gallstone disease account for approximately 80% of cases with AP. It remains uncertain whether gallstones merely initiate or also maintain biliary pancreatitis. Most gallstones that cause AP pass spontaneously through the ampulla of Vater into the duodenum and subsequently can be recovered in the feces within a few days. There has been much interest in early surgical and endoscopic removal of gallstones that are retained in the common bile duct. Although endoscopic retrograde cholangio pancreaticography (ERCP) has no role in the initial diagnosis of acute pancreatitis, there is evidence that early endoscopic sphincterotomy with the aim to remove obstructing stones is the procedure of choice in patients with cholangitis or

with impacted stones. It is the obstruction of the pancreatic duct that causes the onset of AP, and in most cases biliary stones are the offending agent that inhibits the flow of pancreatic juice. In rare cases also parasites like *Ascaris, Fasciola* or *Clonorchis* can be the underlying cause for the development of AP when they migrate into the papilla. In acute biliary pancreatitis, associated cholangitis can contribute to the severity and mortality of the disease, and this is treated best by removing the stones from the common bile duct. In cases of severe biliary pancreatitis (in contrast to severe alcoholic pancreatitis), diagnostic endoscopic retrograde cholangiography (ERC) should be performed within 48 to 72 hours of admission. To discriminate between different etiologies of AP, laboratory tests and diagnostic imaging should be employed initially. With the steadily increasing diagnostic sensitivity of ultrasound, many cases of AP that previously were considered idiopathic now are found to be associated with gallstones or biliary sludge. In view of the current literature, biliary pancreatitis is established when gallstones or gallbladder sludge are detected by ultrasound, and subsequently, ERC should be performed. The sensitivity for the detection of intraductal stones by transabdominal ultrasound is, however, limited, not only because of intestinal air. Additionally, this requires much training and expertise. If ERC is indicated, a cannulation of the pancreatic duct should be avoided, but accidental cannulation of the pancreatic duct does not affect the clinical course or outcome negatively. If gallstones or sludge are found in the common bile duct or at the papilla of Vater, endoscopic sphincterotomy is performed. Although the procedure is associated with a distinct rate of complications (between 6% and 9%), removal of gallstones from the papilla affects prognosis so significantly that sphincterotomy often is attempted even in questionable cases of gallstone impaction. When the offending gallstone already has passed into the duodenum, emergency sphincterotomy is no longer necessary. The passage of a gallstone through the biliary tract generally leads to functional sphincter stenosis rather than insufficiency [43]. This, however, is a transient phenomenon and does not warrant sphincterotomy. Although it is unequivocal that impacted gallstones at the papilla ought to be endoscopically removed, controversy remains about the timing, indication, and patient selection for emergency ERC. One study would include all patients with suspected gallstone pancreatitis in the group for emergency ERCP [44], one only patients with cholestasis (bilirubin levels above 5 mg/dL) [45], and a third only patients with severe disease [46]. When 26 patients with biliary pancreatitis are treated with ERC and sphincterotomy, one life is assumed to be saved [47].

Obsolete treatment concepts

Inhibition of proteolytic enzymes

Although the pathobiology of AP is not fully understood, there is little doubt that in the early phases of the disease, a critical mechanism involved

in pancreatic damage is intracellular, premature, and uncontrolled activation of pancreatic enzymes. For this reason, the inhibition of protease activity has been considered as a potentially beneficial treatment. Several broad-spectrum antiproteases and specific enzyme inhibitors have been tested in experimental studies and shown to have a beneficial effect if administered before the disease onset. In contrast to the promising results from animal studies, two multi-center trials on the use of broad-spectrum protease inhibitors failed to show a positive effect on the clinical course of AP in patients [48,49]. The reason for the failure of antiprotease treatment is probably that premature zymogen activation occurs in the first minutes of the development of pancreatitis when prophylactic treatment would still be effective. This could, in fact, be shown in a study of Gabexate for the prevention of ERCP-induced pancreatitis [50]. Once, however, the disease process is initiated and patients are referred to a hospital hours of even days after the initial event, protease inhibition would no longer be expected to be effective and is, indeed, not [49]. Therefore in clinical practice, protease inhibition is no longer recommended for the treatment of AP (Table 2).

Inhibition of pancreatic secretion

The term autodigestion, introduced by Chiari in 1896, describes the process of proteolytic digestion of the gland by its own enzymes. One way of inducing this process would be hyperstimulation of exocrine pancreatic secretion. Therefore one therapeutic concept for the treatment of AP has been the inhibition of exocrine pancreatic secretion. Experimental and clinical studies have shown that during the course of AP, exocrine secretion is blocked pathologically, and blockage of secretion is an underlying triggering mechanism for several varieties of the disease including gallstone pancreatitis. It is therefore not surprising that clinical studies with the aim to block exocrine secretion could not show any therapeutic benefit. Moreover, a logical consequence of these findings would be that restoring pancreatic secretion, rather than inhibiting it, would be a much more promising treatment strategy. Secretin is the only therapeutic agent that was studied in this area, but in people, secretin only stimulates the secretion of bicarbonate, water, and ions but not of pancreatic enzymes. It was not found to be beneficial in pancreatitis.

Immunomodulation as a treatment in acute pancreatitis

Platelet activating factor (PAF) is a potent phospholipid mediator that is involved in a range of physiological and pathological events. It has been found to play an important role in the pathogenesis of various inflammatory disorders, including AP. The recent development of potent PAF receptor antagonists has led to great advances in understanding the role of PAF in different disease processes and has shown their potential as a promising new therapy for a diverse group of inflammatory disorders.

Table 2
Enzyme inhibitors tested in acute pancreatitis treatment

Broad-spectrum antiproteases	Selective enzyme inhibitor
Aprotinin (Trasylol)	THL (lipase inhibitor)
Gabexate mesilate (Foy)	ONO5046 (PMN-elastase inhibitor)
Camostate (Foy 305)	C1 INH (C1-esterase inhibitor)
Nafamostate mesilate (FUT 175)	AT3 (antithrombin III inhibitor)
Sepimostate (FUT 187)	CaNa2 (phospholipase A2 inhibitor)
Ulinostatin	Procaine (phospholipase A2 inhibitor)
E 3123	Lexipafant (PAF inhibitor) ONO 3307

By enhancing the transmigration of activated polymorphonuclear leucocytes from postcapillary venules into the pancreas, PAF is thought to exert its pathobiological effect during pancreatitis. Once within the interstitial space of the pancreas, activated leukocytes release a variety of proteolytic enzymes and superoxide ions that cause tissue damage. The infusion of antineutrophil serum or PAF antagonists leads to a reduced transmigration of neutrophils and a diminished rate of pancreatic damage [51]. The systemic inflammatory reaction in AP was reduced significantly after application of a PAF antagonist [52]. In view of this evidence from animal studies, the PAF Lexipafant has been tested in a phase II trial for human AP. In this randomized placebo-controlled, multi-center, double-blind study on 290 patients with severe AP (APACHE II score greater than 6), Lexipafant at a concentration of 100 mg intravenously every 24 hours for 7 days did not affect the rate of multi-organ failure. To antagonize the effect of PAF alone was not sufficient to ameliorate SIRS (systemic inflammatory response syndrome) in this disease. In a retrospective evaluation of the study, the authors concluded that the reason for the failure of Lexipafant to show a beneficial effect was that the predominant number of patients included in
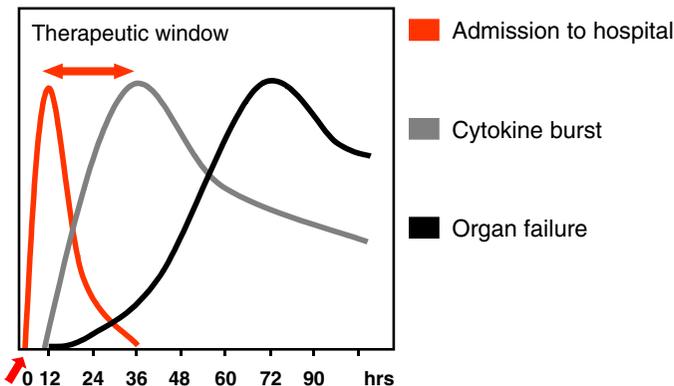

Fig. 2. Time window for effective treatment of acute pancreatitis by immunomodulatory agents or antiproeases before established organ failure occurs [54].

the study had already developed multi-organ failure before the beginning of treatment.

To successfully employ immunomodulation as a concept for the treatment of AP, the respective agent needs to be applied at a very early stage of the disease process. Only a small fraction of patients diagnosed with AP admitted to a primary care center thus would benefit from this form of treatment (Fig. 2) [53].

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