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# Treatment of Acute Pancreatitis: An Attempted Historical Review

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**Key Words**
Acute pancreatitis · Principles of treatment · Intensive therapy · Surgical treatment · Conservative treatment

**Abstract**
This attempt at a historical review of the treatment of acute pancreatitis summarizes the findings of studies carried out in decades long past and shows their impact on the therapy of this disease today. It identifies in retrospect the correct avenues of research and the blind alleys, and describes the ebb and flow of interest in various forms of management. Acquaintance with the work of previous investigators may prevent the unnecessary rediscovery of old principles of treatment. Not all of the studies discussed can be found with search engines: they come from the author's personal library, collected over his 40 years as an active pancreatologist, and from the knowledge of the early literature bequeathed to him by his teachers and mentors.



A review article summarizes the findings of all available studies on a given topic in order to portray the current state of knowledge and recommend ways of increasing knowledge. A historical review, however, summarizes investigations conducted long ago when the disease concerned was first being studied, identifies in retrospect the correct avenues of research and the blind alleys, recalls medical pioneers and their ideas (although this particular historical review has had to leave some unmentioned on grounds of space), and helps to prevent the unnecessary rediscovery of old principles.

The few such reports on the pancreas concern themselves almost exclusively with the discovery of the organ and its diseases and/or with particular aspects of treatment [1–3]. This review is dedicated to all aspects of the treatment of an originally often fatal disease and aims to show the ebb and flow of interest in the various forms of therapy, as well as describe the early findings that retain validity today.

## Principle of Minimizing Toxicity

*Removal of Necroses as Source of Toxicity*

It was clear from the outset that acute pancreatitis can be divided into the relatively harmless edematous or interstitial form and the initially often fatal necrotizing form. The necroses were thought to have a toxic effect on the course of the disease. However, the diagnosis of acute pancreatitis was very difficult.

In the absence of laboratory tests and imaging procedures, clinical examination was crucial. Diagnostic pointers were a history of biliary colic, obesity, occurrence of the first symptoms after consumption of a large meal, se-

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**Table 1.** Mortality following the transition from surgery at any price to active conservative therapy of acute pancreatitis

| Authors | Mortality, % | |
|---|---|---|
| | surgery at any price | active conservative therapy |
| Nordmann [4] | 50 | 24.0 |
| Demel [13] | 78 | 26.4 |
| Paxton and Payne [14] | 45 | 27.5 |
| Total | 58 | 25.3 |

**Table 2.** Indications for surgical management in patients with necrotizing pancreatitis and surgical goals in necrotizing pancreatitis [22]

| |
|---|
| *Indications for surgical management in patients with necrotizing pancreatitis* |
| Morphological criteria |
| – Infected necrosis |
| – Extended intrapancreatic necrosis (>50%) |
| – Intra- and extrapancreatic necrosis |
| – Intestinal perforation/stenosis of the colon |
| Clinical criteria |
| – Severe organ complication (>3 days) in spite of optimal intensive care treatment |
| – Pancreatic abscess |
| *Surgical goals in necrotizing pancreatitis* |
| – Resection of necrotic tissue |
| – Removal of pancreatic ascites from the lesser sac and peritoneal cavity |
| – Arrest of the inflammatory and/or necrotizing processes |
| – Arrest of the release and systemic spread of vasoactive substances |
| – Drainage of bacterially infected areas |
| – Preservation of functional pancreatic tissue |
| – Cure of cholelithiasis |

vere cyanosis, and possibly hematemesis. Acute pancreatic necrosis was confirmed by the presence of initial shock [4], so the diagnosis became clear only late in the disease course.

Once acute necrotizing pancreatitis had been diagnosed with the aid of the few means at hand, it was considered absolutely necessary to operate immediately and remove the necroses. The surgical treatment initially comprised opening the abdominal cavity to drain off an exudate [for example 5]; it was only later that surgical interventions were performed on the pancreas itself.

One of the first to recommend surgical intervention for pancreatitis was the Chicago surgeon Nicholas Senn [6] cited by Rocha et al. [7]. At that time, in the 1880s, pancreatitis was believed to be the response of the pancreas to duodenal disease. Senn recommended drainage and removal of all necrotic tissue. This principle held sway for several decades. In what was probably the largest study of the time, Schmieden and Sebening [8] reported on 1,278 patients with acute pancreatitis, of whom 654 died, representing a mortality of 51.2%. The authors recommended operation over observation, but described the pancreas as an organ inimical to surgery. Right up to the 1940s, the main cause of death in acute pancreatitis was circulatory shock, undoubtedly a consequence of ignorance of the modern principles of intensive care medicine [9]. Even then, however, some voices warned against operating unnecessarily [10]. Morton [11] found that patients with interstitial pancreatitis, then known as 'acute pancreatic edema', were best left in peace. If operated upon, 27% of them died. Nordmann [4] gained the impression that a surgical procedure accelerated the development of necrotizing pancreatitis; this too was perhaps a consequence of the lack of intensive therapy. Nordback et al. [12] later confirmed what many surgeons reported, namely that the macroscopic appearance of the gland correlated poorly with its histology. Parenchymal necrosis varied from 0 to 100% of the resected specimen, although at operation all the glands were considered totally or subtotally necrotic. In other words, a large number of surgeons found it hard to distinguish pancreatic and extrapancreatic necroses intraoperatively.

The unsatisfactory results of operative treatment led to a move away from surgery at any price towards active conservative therapy [10]. This achieved the first decisive reductions in mortality [4, 13, 14] (table 1). The lowering of the overall mortality of necrotizing pancreatitis from around 50% to ca. 25% was a great leap forward.

In the 1960s and 1970s, the pendulum swung towards rapid operative intervention after diagnosis, but with distinct differences from country to country. In the UK, Watts [15] was the first to successfully perform resection of the head of the pancreas in hemorrhagic necrotizing pancreatitis. Early resection, right up to total pancreatectomy, was also recommended in France [16–19]. In Germany, the Mainz group first advised early operation, i.e. necrosectomy soon after admission [20], and later recommended delayed surgery in order to be able to at least approximately demarcate the necroses [21].

In the middle of the 1980s, Germany and many other countries followed the indications for surgical management und surgical goals formulated by Beger and his group [22] (table 2). The principles of intensive care medicine began to become established. With regard to the pancreas, generous administration of fluids, particularly of human albumin, was a breakthrough [23, 24].

In recent years, the pendulum has swung back towards conservative treatment. The conservative management of infected necrosis complicating severe acute pancreatitis was reported [25–27]. At the present time, the best treatment of infected pancreatic necrosis is unclear: conservative, minimally invasive surgery, or open surgery. A study by Runzi et al. [27] investigated 16 severely ill patients with acute pancreatitis who were treated conservatively, including early antibiotic prophylaxis. Only 2 (12%) patients died. A number of minimal invasive measures have been practiced or suggested for the resection of pancreatic necrosis. The first case series of a transluminal endoscopic surgical intervention was reported in 2000, namely transluminal endoscopic debridement of pancreatic necrosis [28]. These investigations seem to represent a first step towards natural orifice transluminal endoscopic surgery [29]. Options for surgical techniques are the resection of necrosis such as open necrosectomy, laparoscopic necrosectomy, staged necrosectomy (e.g. open staged lavage and closed continuous lavage). These procedures are to some extent complementary rather than competing with each other, but surgeons also often differ in their philosophy. However, they agree that surgical intervention – if at all – should be delayed to the later stages of acute pancreatitis [30].

*Principle of Removal of Toxic Substances: Peritoneal Lavage*

Corresponding with general clinical experience, it was observed that patients with acute pancreatitis and severe abdominal pain became pain-free immediately after the beginning of peritoneal lavage. This gave rise to the idea that toxic substances could be removed by means of lavage, and thus that lavage could represent a treatment not only for renal insufficiency (a complication of acute pancreatitis), but also for pancreatitis itself. Following the development of a dialysis procedure applicable to rats [31], continuous peritoneal dialysis performed as a treatment for acute experimental taurocholate pancreatitis in the rat significantly prolonged the mean duration of survival and reduced the mortality rate of this experimental disease [32]. Pancreatic ascites fluid given intravenously led to a sharp decrease in blood pressure in healthy dogs [33, 34]. The reason for this effect was unknown, but it was proposed to be partly due to histamine [35, 36]. In a similar experiment, ascites fluid given intraperitoneally also led to a decrease in blood pressure [37]. No follow-up studies were conducted to identify which toxic substance(s) actually led to the fall in blood pressure.

Eight randomized prospective clinical trials evaluating the influence of continuous peritoneal lavage in patients with acute pancreatitis were performed, but led to divergent results [38–45]. A meta-analysis, however, showed that this therapeutic procedure was not associated with any improvement in mortality or morbidity [46]. Furthermore, attempts were made to enhance the efficacy of peritoneal lavage by adding protease inhibitors to the lavage solution. However, neither of two clinical randomized trials showed any significant differences in mortality and morbidity [47, 48].

## Principle of Inhibition of Secretion

Putting the pancreas at rest in acute pancreatitis became a cardinal principle in the 1960s and 1970s. The goal was either to inhibit gastric secretion, thereby indirectly influencing pancreatic secretion, or to inhibit pancreatic secretion directly.

*Indirect Inhibition*

Following reports of possible triggering of acute pancreatitis by cimetidine in the 1970s [49], animal experiments were carried out to ascertain whether this $H_2$ receptor antagonist could be harmful. Hadas et al. [50] found that cimetidine increased the mortality of sodium taurocholate pancreatitis in rats tenfold. However, these findings could not be duplicated in other animal studies [51, 52]. A meta-analysis carried out several years ago [53] covered five randomized controlled trials written in English comparing the effects of $H_2$ receptor antagonists with those of placebo [54–58]. This meta-analysis [53] showed that cimetidine was not more effective than placebo in reducing acute pancreatitis-related complications and the duration of pain; rather, the use of cimetidine for acute pancreatitis could be associated with higher rates of complications and pain. Thereafter, inhibition of acid secretion was indicated only in severe acute pancreatitis to prevent bleeding from ulcers.

*Direct Inhibition*

Atropine inhibits gastric and pancreatic secretions and exerts a spasmolytic action on the sphincter of Oddi.

These properties would seem to make administration of atropine an ideal therapeutic intervention in acute pancreatitis. These effects cannot be achieved, however, with the dosage that can be administered, i.e. 4 × 0.5 mg/24 h. Higher dosages lead to adverse effects such as amplified symptoms of ileus, tachycardias and atropine psychoses; therefore, particularly after the sole controlled study [59] showed no favorable effect of atropine on the course of acute pancreatitis, this substance was no longer employed. Interestingly, very early reports of the complications of acute pancreatitis included pancreatic encephalopathy, but later, when atropine was no longer used, this adverse effect was not mentioned. Perhaps there is no pancreatic encephalopathy, and the complication that was observed was in fact an atropine psychosis.

Glucagon inhibits the ecbolic and to a lesser extent the hydrokinetic pancreatic secretion. After a first report on the action of glucagon in patients with acute pancreatitis seemed to show a beneficial effect [60], numerous other investigations were conducted. One study showed a favorable influence of glucagon on pancreatitis in pig [61], but this could not be confirmed in other animal models and species [62–66]. Later clinical controlled studies showed no beneficial effect on the course or the mortality of human acute pancreatitis [67–73]. Therefore, the administration of glucagon in acute pancreatitis was abandoned.

Calcitonin, like glucagon, principally inhibits pancreatic enzyme secretion [74]. However, several clinical studies showed no beneficial effect of calcitonin on the course of acute pancreatitis [75–77].

### Principle of Inhibition of Autodigestion

After numerous studies had failed to show any significant decrease in the mortality of patients with acute pancreatitis under treatment with aprotinin [78], one team of investigators [79] was able to reduce the mortality rate considerably by administering a high dose of aprotinin in biliary and idiopathic acute pancreatitis. However, these findings were not confirmed in subsequent trials [67, 69, 73, 80].

The failure of aprotinin, the first antiprotease drug to be used in clinical trials, was attributed to the molecular weight of the substance (6,500 Da), which was considered too high to permit uptake in pancreatic acinar cells and thus inhibition of intracellular proteases. A low-molecular-weight antiprotease, gabexate-mesilate (417 Da), was synthesized and showed promise. However, controlled studies found that this substance was not effective in preventing complications and mortality in acute pancreatitis [81–83]. A meta-analysis on the effectiveness of gabexate-mesilate in acute pancreatitis confirmed that it did not affect mortality or the incidence of complications, including those that required surgery, and thus cannot be recommended [84].

Antifibrinolytics such as ε-aminocaproic acid and its derivatives, transexamic acid, and *p*-aminomethylbenzoic acid inhibit plasmin and trypsin and also increase the antitrypsin activity of plasma. In a single controlled study, ε-aminocaproic acid had no effect on the course of the disease [85].

Treatment of acute pancreatitis with fresh-frozen plasma, given to replenish important circulating proteins, particularly the naturally occurring antiprotease system, seemed to be successful in an uncontrolled study [86]. However, multiple clinical trials of low- and high-volume fresh-frozen plasma therapy showed no differences between treated and nontreated patients [87, 88].

### Principle of Inhibition of Inflammation

Indomethacin inhibits prostaglandin production in vivo and is a very powerful inhibitor of phospholipase $A_2$ activity in serum in patients with acute pancreatitis [89]. In the 1970s, oral or intramuscular administration of indomethacin before or shortly after the triggering of an acute pancreatitis attack in rats markedly reduced mortality [90]. Several years later, in a controlled double-blind study, a Danish group achieved a clear reduction in the frequency and intensity of pain in patients with acute pancreatitis by administering indomethacin suppositories 50 mg twice daily for 7 days [91].

Many years later, the idea of interrupting the inflammatory process with indomethacin and taking advantage of this principle to prevent post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis was put to the test. Several studies [92–94] showed that administering 100 mg indomethacin daily as a suppository could decrease the frequency and severity of post-ERCP pancreatitis. Similar experience has been reported for diclofenac [95]. Although further investigations are necessary [96], administration of indomethacin to ameliorate post-ERCP pancreatitis is a fascinating notion und should be pursued further.

## Principle of Preventing Recurrence

*Role of Weaning from Alcohol*

Although only a small proportion of alcohol abusers ever suffer from acute pancreatitis [97], it is clear that alcohol, after gallstone disease, is the second most frequent cause of inflammation of the pancreas. Patients with a first attack of acute alcohol-induced pancreatitis would thus profit from weaning themselves off alcohol with medical assistance. For decades, however, physicians have adopted a resigned attitude to the problem, and there are no serious systematic, evidence-based studies on this topic. Only now have Nordback et al. [98] shown that repeated interventions at 6-month intervals can significantly reduce the relapse rate of alcohol-induced pancreatitis over a 2-year period. Further studies are of interest.

*Role of Gallstone Removal*

Role of Cholecystectomy

It has long been known that leaving a gallstone-filled gallbladder in situ may result in recurrence of pancreatitis [4], and that cholecystectomy is indicated if an X-ray of the gallbladder (then the only available imaging modality) showed cholelithiasis in nonoperated patients. Decades passed before it was laid down in our guidelines that the cholecystectomy in patients with biliary acute pancreatitis should be performed during the same hospital stay [99–101]. Still now, many think this is of little importance. For decades recurrence of acute pancreatitis was considered harmless compared with the first attack. Only recently was it shown that the second attack of acute pancreatitis is not harmless and that, at least in the case of biliary pancreatitis, such a second attack should be prevented by means of cholecystectomy [102]. However, cholecystectomy to prevent a nonharmless recurrence is carried out in only 23% of cases in Germany [103, 104] and in 51% in the USA, and in the USA there are clear-cut racial differences [105].

Role of Endoscopic Sphincterotomy in Removal of Gallstones of the Common Bile Duct

In the 1930s and 1940s, opening the common bile duct to remove gallstones was a hazardous undertaking. That changed following the development of ERCP, which was first combined with endoscopic sphincterotomy to treat acute biliary pancreatitis in the 1980s [106, 107]. Three controlled studies were published on the role of ERCP with endoscopic sphincterotomy [108–110]. A meta-analysis showed that emergency ERCP with sphincterotomy helps to reduce overall complications and mortality in severe acute pancreatitis [111].

## Conclusions

The greatest change in the treatment of acute pancreatitis is that surgery has been transformed from an immediate measure in necrotizing disease to a late intervention. Although large prospective, multicenter studies are still lacking, the pendulum has swung towards conservative treatment: across the world, conservative measures are tried first even in the presence of infected necroses. Surgical intervention is reserved for complications in the later stages of the disease. Peritoneal lavage has been discontinued owing to its lack of clinical efficacy. It is unfortunate that no investigations were carried out to establish which substances are responsible for the hypotensive action of ascites fluid; a new principle of therapy might have emerged. The principle of inhibition of autodigestion has been completely abandoned, at least in most countries. The significance of the recently rediscovered indomethacin therapy [112] is unclear as yet. Endoscopic sphincterotomy has an established role, while cholecystectomy to prevent recurrence of biliary pancreatitis is undisputed but is still performed too infrequently. It will be interesting to see what part is played by weaning from alcohol, which shows promising early results.

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