Treatment options for acute pancreatitis

Olaf J. Bakker, Yama Issa, Hjalmar C. van Santvoort, Marc G. Besselink, Nicolien J. Schepers, Marco J. Bruno, Marja A. Boermeester and Hein G. Gooszen

Abstract | This Review covers the latest developments in the treatment of acute pancreatitis. The Atlanta Classification of acute pancreatitis has been revised, proposing several new terms and abandoning some of the old and confusing terminology. The 2012 Revised Atlanta Classification and the determinant-based classification aim to universally define the different local and systemic complications and predict outcome. The most important differences between these classifications are discussed. Several promising treatment options for the early management of acute pancreatitis have been tested, including the use of enteral nutrition and antibiotics as well as novel therapies such as haemofiltration and protease inhibitors. The results are summarized and the quality of evidence is discussed. Finally, new developments in the management of patients with infected pancreatic necrosis are addressed, including the use of the 'step-up approach' and results of minimally invasive necrosectomy.

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Introduction

In 2009 in the USA, >274,000 patients were diagnosed with acute pancreatitis, which makes it the most common gastrointestinal disease for which patients are acutely hospitalized.[1] Costs are estimated to exceed US$2.5 billion annually.[1] The prognosis of patients with acute pancreatitis varies widely and is primarily determined by the presence of organ failure and infected pancreatic necrosis (comprising pancreatic parenchymal necrosis or extrapancreatic necrosis; necrosis is liquefaction of solid tissue through the process of tissue death).[2] Early persistent organ failure is associated with a mortality rate exceeding 30%.[3] Infected pancreatic necrosis has a reported mortality rate of ~15%.[4] Despite increasing incidence,[5,6] no specific drug therapy is available to ameliorate the course of disease, in particular in patients with acute pancreatitis who develop the systemic inflammatory response syndrome (SIRS) early after onset of symptoms and hence are prone to develop organ failure. Treatment of organ failure consists of specific organ supportive measures.[7] In general, treatment of infected pancreatic necrosis consists of drainage or debridement.[8] In the past years, several important changes in disease classification and improvements in the management of patients with acute pancreatitis have been achieved. This Review provides an overview of these changes, the effect on patient management and outcome, and discusses their scientific basis.

Changes in classification

In 1992, a classification system for acute pancreatitis was developed during a consensus conference held in Atlanta, Georgia.[9] 'Atlanta 1992' aimed to universally define the different local and systemic complications that can develop in acute pancreatitis. At the time, the classification was an important step forward; however, some of the definitions turned out to be confusing. A literature review of >400 articles on acute pancreatitis found a different use of the Atlanta definitions in more than half of them.[10] In particular, terms related to the content of peripancreatic collections, such as acute fluid collection, pseudocyst and even pancreatic necrosis, were interpreted differently.[11] As the quality of CT and MRI have increased over the years, so has the understanding of local complications in acute pancreatitis.[12] In addition to improved understanding of local complications, our understanding of systemic complications has also progressed. Systemic complications included in Atlanta 1992, such as a low serum calcium level or low platelet count, were found to be general symptoms of critical illness instead of specific complications of pancreatitis.[10] For these reasons, a clear need to revise the old Atlanta classification became apparent and an international web-based consultation was undertaken. The aim was to provide more objective terms to describe local complications and to uniformly define the systemic complications of this disease.[13]

Difficulties in redefining local complications

The 2012 Revised Atlanta Classification divides acute pancreatitis into three categories: mild, moderate and severe disease.[13] Each of these categories is based on the absence or presence of local or systemic complications (Table 1 and Box 1). Acute pancreatitis is divided into interstitial oedematous and necrotizing pancreatitis. Local complications that can develop are linked to one of the two types. The main argument put forward by the authors of the revised classification to make this distinction is to separate fluid collections containing only fluid from collections that contain a solid component (and thus contain an amount of necrosis).[13] The amount of necrosis is related to specific

Department of Surgery, Room G04.228, University Medical Center Utrecht Heidelberglaan 100, PO Box 85500, 3508 GA Utrecht, Netherlands (**O.J.B.**, **H.C.v.S.**). Department of Surgery (Suite G4-136), Academic Medical Center, Meibergdreef 9, 1105 AZ, PO Box 22660, 1100 DD Amsterdam, Netherlands (**Y.I.**, **M.G.B.**, **M.A.B.**). Department of Gastroenterology & Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, 's-Gravendijkwal 230, 3015 CE Rotterdam, Netherlands (**N.J.S.**, **M.J.B.**). Department of Operation Rooms/ Evidence Based Surgery, Radboud University Medical Centre, Geert Grooteplein zuid 10, PO Box 9101, 6500 HB Nijmegen, Netherlands (**H.G.G**).

Correspondence to: H.G.G. hein.gooszen@radboudumc.nl

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Key points

- The 2012 Revised Atlanta Classification and the determinant-based classifications for acute pancreatitis aim to define the different local and systemic complications of this disease and predict interventions and outcomes
- These different classifications can be viewed as complementary; some of the terminology might need further development to provide more exact definitions
- Several prophylactic strategies have been tested to prevent complications in acute pancreatitis, but no strategy has proved to be successful
- Progress has been made in the management of infected pancreatic necrosis with the use of a step-up approach and minimally invasive techniques

complications that can occur—such as infection of necrosis or pancreatic insufficiency—and thereby determines patient outcome.[14] The proposed distinction seems logical for stratification of patients for treatment and research purposes. However, the most used imaging technique in acute pancreatitis is contrast-enhanced CT (CECT). On the basis of CT images it can sometimes be difficult, if not impossible, to distinguish fluid from necrosis.[12] MRI can clearly distinguish fluid from solid components, but in daily practice MRI is not as easily performed as CT. This limitation of CT to some extent restricts the implementation of the new classification. Also, in the new classification, the different types of local complications are defined according to the time after onset of disease. A cut-off value of around 4 weeks is proposed.[13] For example, acute necrotic collections develop within 4 weeks and are defined as collections containing a variable amount of fluid or necrotic tissue. After 4 weeks, these collections start to become encapsulated by an enhancing wall of reactive tissue and are then named walled-off necrosis. The timing of encapsulation, however, differs markedly between patients and can only be judged on CECT, rather than according to time from symptom onset.[12]

Furthermore, necrotizing pancreatitis is defined as pancreatic parenchymal necrosis or extrapancreatic necrosis in the absence of parenchymal necrosis. The latter is now recognised as a separate entity within the spectrum of morphological features in acute pancreatitis.[15] However, differentiating between an acute peripancreatic fluid collection without necrosis or an acute peripancreatic fluid collection containing necrosis (which thus should be named extrapancreatic necrosis) can be difficult using CECT (Figure 1). Therefore, we recommend following up on these collections during the disease course to differentiate one from the other.

The 2012 Revised Atlanta Classification repeatedly uses the term 'collection'. In the classification, it is used as a broad term including several local complications. However, no definition of 'collection' is given. We suggest that 'collection' should be defined and that this definition should specify whether a collection in the context of a local complication in acute pancreatitis would contain fluid or necrosis. The definition of pseudocysts also seems incomplete. A pseudocyst always contains amylase-rich fluid, so—in our opinion—this requirement needs to be included in the definition. Furthermore, a pseudocyst is lined not by epithelium, but rather by granulation tissue. 'Granulation tissue' is probably a more correct term than 'inflammatory wall', which is used in the 2012 Revised Atlanta Classification. In the context of severe necrotizing pancreatitis, 'collection' is used in the definition of walled-off necrosis. However, necrosis spreads in various degrees throughout the retroperitoneum and into the small and large mesentery as there are no anatomical barriers. If expansive, then the necrosis cannot be said to be co-located into a 'collection'. We suggest that an alternative description would be to divide pancreatic necrosis into pancreatic necrosis that is 'limited' or pancreatic necrosis that is 'expansive'.

Difficulties in redefining systemic complications

Systemic complications are defined as persistent organ failure or an exacerbation of a pre-existing comorbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis attack.[13] However, it can sometimes be very difficult to distinguish whether the acute pancreatitis attack (which might cause SIRS, in turn leading to organ failure) or the exacerbation of the pre-existing comorbidity caused the development of organ failure. One might also argue that as organ failure is already included in the classification, the inclusion of exacerbation of a pre-existing comorbidity in the classification is redundant. On the other hand, patients with pre-existing comorbidity might also be admitted without SIRS, without local complications, without organ failure and still might have a prolonged stay at hospital; for example, pulmonary failure might occur in a patient with chronic obstructive pulmonary disease. This scenario is now considered 'moderate–severe' pancreatitis (that is, when a pre-existing comorbid condition is exacerbated by the pancreatitis attack).

Persistent organ failure (defined as >48 h) is emphasized as the defining feature of severe pancreatitis. Three organ

Table 1 | Classifications of acute pancreatitis

Complications	1992 Atlanta		2012 Revised Atlanta*			Determinant-based classification‡			
	Mild	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Critical
Local complications	No	Yes	No	Yes	Yes	No	Sterile	Infected	Infected
Systemic complications:									
Transient organ failure	No	Yes	No	Yes	No	No	Yes	Yes	No
Persistent organ failure	No	Yes	No	No	Yes	No	No	Yes	Yes
Exacerbation of pre-existing comorbidity	NA	NA	No	Yes	Yes or No	NA	NA	NA	NA

*In Atlanta 2012, several different local complications are distinguished (see also Box 1). Systemic complications are defined as transient or persistent organ failure or an exacerbation of a pre-existing comorbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis attack. Persistent organ failure is defined as organ failure persisting for >48 h. Three organ systems are addressed: respiratory, cardiovascular and renal. Organ failure is defined as a score of ≥2 using the modified Marshall scoring system for respiratory, cardiovascular and renal organ systems. ‡In the determinant-based classification, the SOFA score is used to define organ failure. For severe pancreatitis, either infected pancreatic necrosis or persistent organ failure is mandatory. Abbreviations: NA, not applicable; SOFA, sepsis-related organ failure assessment.

Box 1 | Local complications in acute pancreatitis*

Interstitial oedematous pancreatitis
- Acute peripancreatic fluid collection (peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripancreatic necrosis)
- Pancreatic pseudocyst (an encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis)

Necrotizing pancreatitis
- Acute necrotic collection (a collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma or the extrapancreatic tissues)
- Walled-off necrosis (a mature, encapsulated collection of pancreatic or extrapancreatic necrosis that has developed a well-defined inflammatory wall)

Infected pancreatic necrosis
- Acute necrotic collection
- Walled-off necrosis

Other local complications
- Gastric outlet dysfunction
- Splenic or portal vein thrombosis
- Colonic necrosis

*According to the 2012 Revised Atlanta Classification

systems are addressed in the Atlanta 2012 classification:[13] respiratory, cardiovascular and renal. The modified Marshall scoring system is used to define organ failure in one of these three organ systems.[16] Although proposed as a simple and easy-to-use scoring system, the modified Marshall score has two major disadvantages. First, patients with persistent organ failure are sometimes admitted for >6 months in hospital. It is cumbersome to calculate the modified Marshall score for three separate organ systems on a daily basis throughout the whole disease course. As such, when retrospective cohorts describe the incidence of organ failure with the modified Marshall system, one might question the accuracy of the reported organ-failure rates.[2] Second, endotracheal intubation for respiratory failure, the use of vasopressors for persistent hypotension after fluid resuscitation and renal replacement therapy for renal insufficiency are not considered in the Atlanta 2012 classification; if patients receive these supportive therapies, it might result in normal arterial oxygen measurements and normal systolic blood pressures. Hence, the Marshall score will not reach the threshold for organ failure and these patients would be categorised as having moderate pancreatitis. Despite these minor weaknesses, Atlanta 2012 is again a major step forward and is likely to improve communication between physicians and improve the accuracy of studies that describe cohorts of patients with pancreatitis.

Parallel to the revision of the Atlanta classification, a second initiative was undertaken to likewise redefine acute pancreatitis and its complications.[17] In contrast to Atlanta 2012, the determinant-based classification proclaims to be based on determinants of severity and the epidemiological concept of causal inference. However, when comparing both classifications, a similar subdivision of local and systemic complications is found. Some differences do exist though. For example, organ failure is defined using the sepsis-related organ failure assessment (SOFA) score instead of the modified Marshall score. In addition to the three categories of mild, moderate and severe pancreatitis, a fourth category is proposed: critical acute pancreatitis. This category of acute pancreatitis is characterized by the presence of infected necrosis and persistent organ failure (Table 1).

A head-to-head comparative study has been published comparing Atlanta 1992, Atlanta 2012 and the determinant-based classification.[18] In a single-centre prospective study of 256 patients, severity classification was associated with worse clinical outcomes for all three classifications, and all 10 patients who died had been classified as having severe or critical disease. The least efficient classification system, however, was the 1992 Atlanta Classification, which classified 126 patients as having severe disease, compared with the 2012 Revised Atlanta Classification which classified 65 as severe and the determinant-based classification which classified 49 as severe and 17 as critical. The determinant-based classification performed better in predicting the need for interventions, whereas the 2012 Revised Atlanta Classification performed better in predicting length of hospital stay. Ultimately, the existence of two parallel classifications systems seems conflicting. Widespread implementation of either one of the classifications in daily practice is likely to be limited by their co-existence. The near future will hopefully show which system is to be adopted by the pancreatic community.

New insights into early management

Predicting complications in acute pancreatitis

In the absence of a specific drug therapy for patients with acute pancreatitis, all early management strategies are mainly supportive. As the clinical course varies widely, it is important to predict complications on admission or within 24–48 h thereafter to initiate further management strategies such as early intensive care admission. Scoring systems based on clinical and laboratory values to predict complications (or more specifically, pending organ failure or the development of necrotizing pancreatitis) have been developed in abundance over the years. A head-to-head comparison of the nine most frequently used systems showed a moderate overall efficacy of these scoring systems.[19] The modified Glasgow score[20] was the best classifier on admission with an area under the curve of 0.84 in the training cohort of the study and 0.74 in the validation cohort. Complex combinations of different scoring systems might improve efficacy, but are virtually impossible to implement in daily practice. Perhaps novel approaches might further improve accuracy. These novel approaches would need to include rapid determination of biomarkers of normal and pathophysiologic processes (for example, damage-associated molecular pattern molecules, cytokine levels or physiological measures) together with information on susceptibility for progression to severe pancreatitis (for example, genetic polymorphisms, obesity, alcoholism and pre-existing comorbidity). From 2009 to 2011, a collaboration between research groups from the USA and the Netherlands investigated more simplistic ways to predict complications. Levels of blood urea nitrogen (BUN) on admission and after 24 h seem to be an accurate, readily

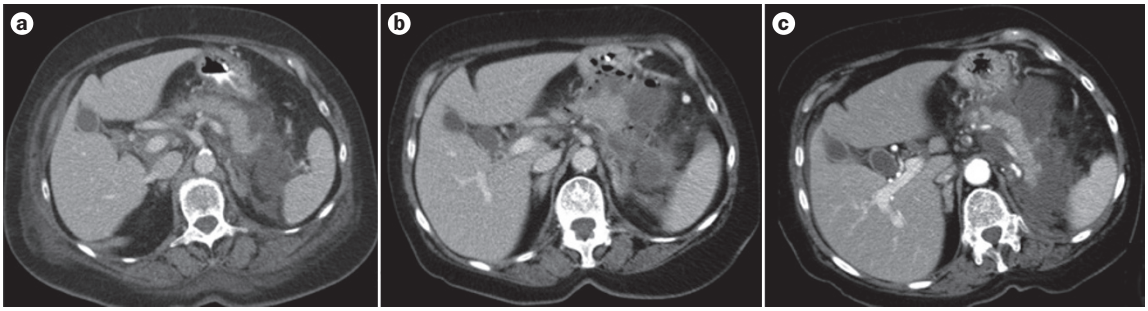

Figure 1 | A patient with acute pancreatitis. **a** | Contrast-enhanced CT image of a patient 1 week after onset of symptoms. The pancreas enhances completely and is surrounded by either an acute peripancreatic fluid collection or extrapancreatic necrosis. Distinguishing between the two is difficult at this point. **b** | The same patient 3 weeks after symptoms onset. The enhancing pancreas is surrounded by a heterogeneous collection of dense fluid and fat. This finding is typical for extrapancreatic necrosis. **c** | The same patient 5 weeks after symptom onset. The patient suddenly developed pain in the upper abdomen. CT demonstrated an acute necrotic collection with a smaller size than the previous CT had shown, and gas bubbles inside the acute necrotic collection. These findings suggested a spontaneous fistula between the acute necrotic collection and the stomach. During endoscopy the fistula was visualized. Subsequently, endoscopic transgastric necrosectomy was performed and the patient recovered.

available, low cost and universal way to predict mortality.[21] A BUN level of 20 mg/dl (or 7.14 mmol/l) is associated with an odds ratio of 4.6 for mortality. Any rise in BUN level within 24 h of admission, irrespective of BUN admission values, is associated with an odds ratio of 4.3 for mortality. Creatinin and haematocrit levels are simple measures to predict the development of pancreatic necrosis.[22] A low level of haematocrit on admission (<45%) has a negative predictive value of 89% for the development of pancreatic necrosis. Creatinin levels >1.8 mg/dl (or 159 μmol/l) within 48 h of admission have a positive predictive value of 93% for the presence of pancreatic necrosis.[22]

Another frequently used predictor with an increasing accuracy beyond 48 h is C-reactive protein.[23] Notably, however, the modified Glasgow score and C-reactive protein level are calculated or measured >48 h after admission, at which time scoring systems or single predictors actually reflect ongoing organ failure instead of predicting pending organ failure.

SIRS can be used to monitor disease progression. A substantial number of patients with acute pancreatitis have SIRS on admission, but persistent SIRS 24–48 h after admission is strongly associated with the development of organ failure.[24] The new International Association of Pancreatology and American Association of Pancreatology (IAP/APA) guideline advises repetitive monitoring of the presence of SIRS during the first days of admission.[7]

Early supportive measures

Fluid therapy

Probably the most important component of early supportive measures in patients with acute pancreatitis is fluid supplementation. Third-spacing—accumulation of fluid in the third space (the non-functional area between cells where fluid does not normally accumulate in large amounts)—can cause intravascular hypovolemia and might evoke organ failure. Liberal fluid supplementation to correct or preferably prevent intravascular hypovolemia is commonly accepted as the first step in supportive care. A practical approach for the amount of fluids to administer would be bolus infusion of 20 ml per kg of body weight of Lactated Ringer's solution (which is isotonic with blood) in the emergency department followed by a total infusion of ~2,500–4,000 ml in the first 24 h after admission.[7,25] Vital signs, physical examination and urine output should be repeatedly assessed every 6 h. After 24 h, fluid resuscitation can be tailored according to vital signs and urinary output. If any signs of organ dysfunction arise despite adequate resuscitative measures, we strongly advise to consult an intensive care specialist. Although only a minority of all patients with acute pancreatitis develop organ failure during the first 72 h after admission, it is crucial to recognise these patients early.

Nutrition

Nutritional support is nowadays considered a therapeutic measure instead of merely a way to provide calories in a patient with severe pancreatitis. Enteral nutrition through a nasoenteric feeding tube has been shown to reduce organ failure, infected necrosis and mortality compared with parenteral nutrition.[26] These complications are thought to be mediated by bacterial translocation from the gut provoked by disturbed intestinal motility, bacterial overgrowth and increased mucosal permeability.[27–29] Enteral nutrition is believed to stimulate intestinal motility—thus reducing bacterial overgrowth—and is believed to increase splanchnic blood flow, which helps to preserve the integrity of the gut mucosa.[30,31] The improved outcomes found in the trials following the use of enteral nutrition might also be the result of complications specifically related to parenteral nutrition, such as catheter-related infections.[32]

The optimal timing to start enteral nutrition has not been fully established. It used to be common practice to start enteral nutrition after a few days if an oral diet is not tolerated. However, evidence is growing that early initiation (within 24–48 h of admission) of enteral tube feeding considerably improves outcome; a small randomized trial, a retrospective study and two conventional meta-analyses (based on studies investigating route of nutrition instead of timing of nutrition) conclude that early enteral nutrition

reduces complications compared with enteral nutrition started after >48 h.[33–36] On the basis of these studies, in patients with severe pancreatitis, enteral nutrition should be started within 24–48 h after admission. However, a large multicentre randomized trial compared very early nutrition (within 24 h) through a nasoenteric feeding tube to nutrition-on-demand with an oral diet started 72 h after admission and nasoenteric tube feeding only if necessary;[37] results showed that early enteral nutrition was not able to reduce the composite end point of infections or mortality (unpublished data, O.J.B.).

Antibiotics

Prophylactic administration of intravenous antibiotics has been used with the aim to prevent infected necrosis and other infectious complications. Several randomized trials have shown that routine use of antibiotics does not prevent infected necrosis.[38] Therefore, antibiotics in acute pancreatitis are indicated in case of proven infection or in case of a very strong clinical suspicion of cholangitis or infected necrosis.[7]

Endoscopic retrograde cholangiopancreatography

Urgent endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy is indicated in patients with biliary pancreatitis and concomitant cholangitis, whereas ERCP is not indicated in patients with mild biliary pancreatitis.[7,39] The verdict of whether ERCP with sphincterotomy should be performed routinely in patients with predicted severe biliary pancreatitis without cholangitis is still undecided. Current meta-analyses and guidelines show conflicting results.[40] Although several randomized trials have been published on this matter, the optimal policy for patients with predicted severe biliary pancreatitis but without cholangitis cannot be extracted as these trials also included patients with mild pancreatitis or with cholangitis.[41–44] A multicentre randomized trial including this specific group of patients has started recruitment.[45]

Novel therapies in acute pancreatitis

Haemofiltration and peritoneal dialysis

In severe pancreatitis, a local inflammatory process climaxes into systemic inflammation with concomitant organ failure. Proinflammatory cytokines as mediators of inflammation are believed to have an important role in the exacerbation of the disease.[46] A potential new therapeutic measure in acute pancreatitis is the elimination of these mediators with the use of continuous venovenous haemofiltration or peritoneal dialysis.[47] Two small Chinese trials randomly allocated patients with severe acute pancreatitis to haemofiltration with or without peritoneal dialysis or to standard therapy without haemofiltration or peritoneal dialysis.[48,49] Therapy was started daily during 4–6 h from hospitalization. Reported results seem promising; after haemofiltration and peritoneal dialysis, levels of all cytokines dropped substantially sooner, the time to relief of abdominal pain was shortened, CT severity scores decreased, APACHE II (acute physiology and chronic health evaluation; a measure of disease severity) scores decreased, and the incidence of organ failure was decreased compared with controls.[48,49] Unfortunately, detailed insight into the early therapeutic strategy is lacking (for example, how many patients had failed attempts at haemodialysis during the first days of severe pancreatitis, when patients can be haemodynamically unstable). In addition, some other methodological weaknesses of the studies (for example, the analyses were not based on the intention-to-treat principle, no adverse events were reported and no information on end point adjudication was provided) hamper the validity of the results. So far, no convincing evidence has been produced to justify widespread application of these blood purification techniques. Hopefully, in the near future, insights into the efficacy of this therapeutic measure will be broadened.

Continuous infusion of a protease inhibitor

One of the possible mechanisms of the development of pancreatic necrosis is thought to be microvascular obstruction caused by local vasospasm and increased intravascular coagulability.[50] Experimental studies have shown that intra-arterial protease inhibitors can inhibit the coagulation system, inhibit proteases such as trypsin (a pancreatic enzyme), and have other effects such as inhibition of cytokine production.[51] The use of protease inhibitors combined with antibiotics might prevent secondary infection of pancreatic necrosis by facilitating the delivery of antibiotics into the pancreatic tissue. Several studies have investigated the effect of protease inhibitors in acute pancreatitis. A study from Poland randomly allocated 78 patients to either continuous regional arterial infusion with protease inhibitors and antibiotics or to standard treatment without proteases but with antibiotics.[52] Although no differences were found in infectious complications, mortality after infusion of a protease inhibitor was significantly reduced ($P=0.02$). In line with the first positive results after haemofiltration in acute pancreatitis, these first positive results are also criticized owing to methodological weaknesses. Potential baseline differences, no reporting of infected pancreatic necrosis and organ failure as outcomes, the long recruitment period (6 years) and high drop-out rates are several of these weaknesses. Despite the lack of convincing evidence, protease inhibitors have been recommended in the Japanese guidelines for treatment of acute pancreatitis for several years.[53] An in-patient registration study including >1,000 Japanese hospitals investigated mortality after infusion of protease inhibitors and used propensity-score matching to compare outcomes with controls.[54] Unfortunately, continuous regional infusion of protease inhibitors was not able to reduce mortality. By contrast, hospital stay was prolonged and costs were increased with the use of protease inhibitors. These conflicting results probably provide enough clinical equipoise for a large clinical trial on the use of protease inhibitors. However, it is unlikely that such a trial will be feasible in the near future as patients with severe pancreatitis are always admitted acutely instead of electively; furthermore, protease inhibitors need to be administered very early in disease progression, which is logistically difficult, and single institutions only admit a few patients with severe pancreatitis per year, which complicates accrual rates.

Management of infected necrosis

Delaying interventions

The question of when to intervene in patients who have suspected or proven infected pancreatic necrosis has puzzled pancreatologists for years. Very early surgical intervention (that is, within 72 h after admission) is clearly harmful.[55] In series describing results after interventions for necrotizing pancreatitis, intervention is performed after a median of ~4 weeks after onset of symptoms (either drainage or necrosectomy).[56,57] Postponement of intervention theoretically provides an opportunity for acute necrotic collections to become walled-off and for the necrosis to liquefy. This process facilitates necrosectomy and probably improves the outcome of invasive interventions such as percutaneous catheter drainage (PCD), endoscopic transluminal drainage or surgical or endoscopic necrosectomy. However, in severely ill patients, if intervention is deemed necessary, this should not be postponed just to wait for encapsulation.

Step-up approach

PCD might be performed as the first step in treatment of infected pancreatic necrosis, followed by necrosectomy only when the patient does not improve. The PANTER trial showed that this approach reduces new-onset organ failure and prevents the need for necrosectomy in about a third of patients compared with primary necrosectomy.[58] This so-called step-up approach could be considered the standard approach to treating infected pancreatic necrosis.[7,8] Whether the first step (that is, drainage), should be performed endoscopically or percutaneously, is the subject of ongoing research and probably also depends on local expertise. Endoscopic transluminal drainage has the theoretical advantage of preventing the development of an external pancreatic fistula as compared to PCD. Such fistulas prolong hospital stay, are cumbersome for patients and can sometimes be difficult to treat.[59] Internal drainage of a pancreatic fistula can enhance recovery.

Minimally invasive surgery or endoscopy?

The traditional approach for necrosectomy is open surgical necrosectomy with complete removal of all infected pancreatic necrosis.[60] The rate of reported complications such as mortality, new-onset organ failure and need for intensive care admission after open surgery vary between institutions, but are reported in up to 80% of patients.[56] Minimally invasive techniques such as video-assisted retroperitoneal debridement or minimal access retroperitoneal pancreatic necrosectomy might reduce complications.[56,61–63] Endoscopic necrosectomy, using a transgastric or transduodenal approach, is theoretically even less invasive. It is a form of natural orifice transluminal endoscopic surgery (NOTES) and can be performed under conscious sedation without the need for general anaesthesia. A randomized pilot trial comparing surgical to endoscopic necrosectomy showed a reduced proinflammatory response after endoscopic necrosectomy.[64] Interestingly, a reduction in the composite end point of death and major complications was also found following endoscopic necrosectomy. These promising but preliminary results require urgent validation.

A multicentre randomized trial has started comparing an endoscopic approach with a surgical step-up approach in patients who have infected pancreatic necrosis (TENSION trial).[65] Until results are available, the method and route of drainage and necrosectomy depend largely on local experience available in each institution. Interactive collaboration between surgeons, gastroenterologists, intensivists and radiologists is crucial in the treatment of these complex subgroups of patients, with regard to the use of supportive measures and type and timing of interventions to manage infected pancreatic necrosis.

Conclusions

Despite the promising results of numerous experimental and small clinical studies in acute pancreatitis, ultimately all adequately powered clinical trials in acute pancreatitis validating these early results turned out negative. Antibiotics, probiotics, anti-inflammatory drugs such as lexipafant, and even early enteral nutrition have all been tested and do not improve clinical outcome.[66–68] From these findings we need to conclude two things. First, all promising results from small studies require validation in large scale trials. Second, an urgent need still exists for new therapeutic agents. In a disease with increasing incidence and already >270,000 admissions each year in the USA,[1] a strong collaborative platform is needed to rapidly test new therapeutic agents. Randomized trials remain the most powerful tool to evaluate the effectiveness of new agents while accounting for unmeasured confounders or selection bias. However, large randomized trials are very complex, costly and require considerable time to recruit patients. A new tool for the pancreatic community might be the registry-based randomized trial.[69] With the use of large-scale, low-cost observational registries, new randomized trials can be performed with considerably less cost, in less time and in a real world population. Unfortunately, no large-scale registries for patients with acute pancreatitis exist thus far. So, the first logical step would be to start enrolling patients in observational registries across multiple international sites. Once these registries are ongoing, they might provide a potent platform for the testing of new therapeutic agents. As acute pancreatitis will probably cause increasing mortality and increasing costs in future years, new therapeutic agents are very much needed.

Review criteria

We searched the PubMed database using the terms "acute pancreatitis" combined with "classification", "mortality", "infection", "necrosis", "nutrition", "protease inhibitors", "haemofiltration", "minimally invasive", "necrosectomy", "endoscopy" and "surgery". We selected full-text articles in English from the past 10 years, but exceptions were made for older highly cited papers. We aimed to describe results of randomized controlled trials, but other studies are also referenced. In addition, reference lists of articles were manually searched. Some of the recommendations in this Review are based on the recently revised guidelines of the International Association of Pancreatology (IAP) and the American Pancreatic Association (APA).

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Author contributions

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